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Europäisches Patentamt
European Patent Office
Office européen des brevets

Publication number:

0 097 023
A2

12

EUROPEAN PATENT APPLICATION

21 Application number: 83303321.0

51 Int. Cl.³: **C 07 C 177/00, A 61 K 31/557,**
C 08 B 37/16

22 Date of filing: 08.06.83

30 Priority: 10.06.82 JP 98414/82

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43 Date of publication of application: 28.12.83
Bulletin 83/52

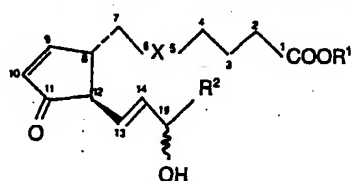
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84 Designated Contracting States: **AT BE CH DE FR GB IT**
LI LU NL SE

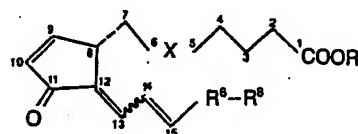
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54 Prostaglandin D derivatives, process for their preparation and compositions containing them.

57 Prostaglandin D derivatives of the formula:

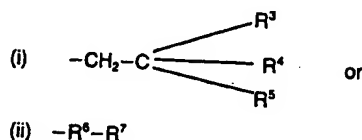


(I)



(II)

wherein R¹ is hydrogen or alkyl, R² is a group of the formula:



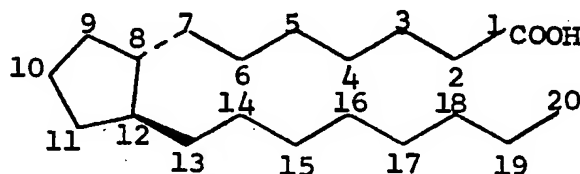
wherein R³ is alkyl, R⁴ is hydrogen or alkyl, R⁵ is alkyl R⁶ is a single bond or alkylene, R⁷ is cycloalkyl, X is ethylene or cis-vinylene, the double bond between C₉—C₁₀ is Z, and the double bond between C₁₃—C₁₄ is E, or of the formula:

wherein R¹, R⁶ and X are as hereinbefore defined, R⁵ is alkyl, cycloalkyl, phenyl or phenoxy, the double bonds between C₁₂—C₁₃ and between C₁₄—C₁₅ are E, Z or a mixture thereof, and the double bond between C₉—C₁₀ is Z, provided that when R⁶ represents a single bond, R⁵ does not represent a substituted or unsubstituted phenoxy group, and cyclodextrin clathrates and non-toxic salts thereof, possess anti-tumour activity.

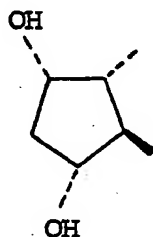
DESCRIPTION"PROSTAGLANDIN D DERIVATIVES, PROCESS FOR THEIR PREPARATION
AND COMPOSITIONS CONTAINING THEM"

The present invention relates to novel prostaglandin D derivatives, to processes for their production and pharmaceutical compositions containing them.

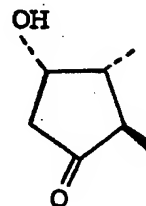
- 5 Prostaglandins are derivatives of prostanoic acid having the following structure:



- Various types of prostaglandins are known, and their types depend on the structure of the alicyclic ring and the substituents. For example, the alicyclic rings of prostaglandin F (PGF), E (PGE) and D (PGD) have the following structures, respectively:

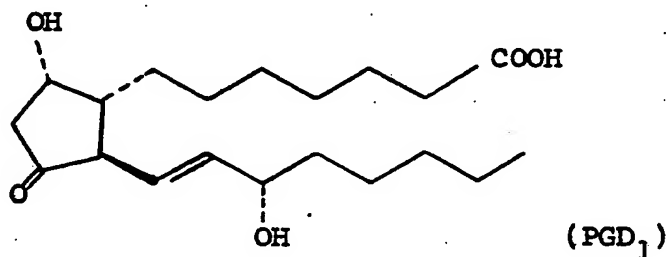


and

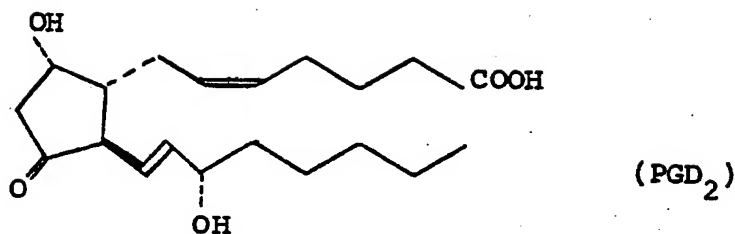


In the above structural formulae or in the other structural formulae in this specification, according to the generally accepted nomenclature, the broken line indicates that the substituent attached thereto is behind the ring plane, i.e. is of the α -configuration, the bold line indicates that the substituent attached thereto is in front of the ring plane, i.e. is of the β -configuration, and the wavy line indicates that the substituent attached thereto is of the α -configuration or the β -configuration or a mixture thereof.

These compounds are sub-classified according to the positions of the double bonds in the side chains attached to the alicyclic ring at the 8-position and the 12-position. The PG-1 compound has a trans double bond (15) (trans- Δ^{13}) between C_{13} - C_{14} and the PG-2 compound has a cis double bond between C_5 - C_6 and a trans double bond between C_{13} - C_{14} (cis- Δ^5 , trans- Δ^{13}). For example, prostaglandin D_1 (PGD₁) and prostaglandin D_2 (PGD₂) may be expressed by the following structural formulae respectively:



and



Further, when one or more methylene groups are removed from the aliphatic group attached at the 12-
5 position of the alicyclic ring of a prostaglandin, said compound is known as a nor-prostaglandin according to the general rule of the organic nomenclature, and the number of the removed methylene groups is indicated by adding di-, tri- etc. before the prefix "nor".

10 The prostaglandins generally have pharmacological properties. For example, they exert various effects, including the stimulation of contraction of smooth muscles, a hypotensive effect, a diuretic effect, a bronchial
15 dilation effect, the inhibition of lypolysis, the inhibition of platelet aggregation and the inhibition of gastric acid secretion. Therefore, they are useful in treatments of hypertension, thrombosis, asthma and gastric and intestinal
20 ulcers, in the induction of labor and abortion in pregnant mammals, in the prevention of arteriosclerosis and also as diuretics. They are liposoluble substances present in extremely small quantities in the tissues which secrete prostaglandins in vivo in animals.

As a result of research and experimentation to discover novel compounds which have the pharmacological effects of the "natural" prostaglandins, or which have one or more of these properties to an enhanced degree, 5 or which have properties which are not found in the "natural" prostaglandins, it has been discovered that novel compounds in which the hydroxy group attached at the 9-position and the hydrogen atom attached at the 10-position of PGD_1 and PGD_2 have been removed to introduce 10 a cis double bond between $\text{C}_9 - \text{C}_{10}$ (9-deoxy- Δ^9 -PGD analogues) and related novel compounds in which, in addition, the hydroxy group attached to the 15-position has been removed to introduce double bonds between the $\text{C}_{12} - \text{C}_{13}$ and $\text{C}_{14} - \text{C}_{15}$ positions have a surprisingly 15 strong anti-tumour effect whereas they have no or very weak pharmacological properties possessed by the "natural" prostaglandins.

The fact that PGD_2 inhibits the proliferation of cancerized mast cells has already been made public 20 [see Proceedings of the Japanese Cancer Association, the 40th Annual Meeting (published on September 5, 1981)]. However, the anti-tumour effect of compounds of the present invention which are structurally distinguished from PGD_2 has been found to be superior by several times as compared 25 with that of PGD_2 whereas in other PG-like properties compounds of the present invention are several times less

active than PGD_2 . The compounds of the invention tested therefore exert an anti-tumour effect which is selective in relation to the other effects, a particularly advantageous selective action compared with PGD_2 .

5 Heretofore, there have been filed several patent applications relating to 9-deoxy- Δ^9 -PGD analogues. For example, there are disclosed 9-deoxy- Δ^9 -PGD₂ and alkyl esters thereof in the specification of the United States Patent No. 3954844 (Derwent No. 37947X); compounds
10 wherein various substituents have been introduced into the aliphatic group attached to the 12-position are described in the specification of the United States Patent No. 4016184 (Derwent No. 24680Y); and further compounds in which the carboxyl group at the 1-position of the
15 9-deoxy- Δ^9 -PGD analogues have been replaced by a hydroxymethyl group are described in the specifications of the United States Patent Nos. 4028419 (Derwent No. 43349Y), 4055602 (Derwent No. 48794Y) and 4032576 (Derwent No. 48793Y).

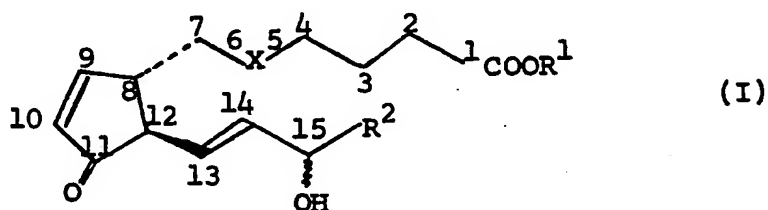
20 However, none of the above applications discloses the compounds of the present invention.

Compounds of the invention which have double bonds between $\text{C}_{12} - \text{C}_{13}$ and $\text{C}_{14} - \text{C}_{15}$ are also novel: compounds having such a structure have not heretofore been
25 discovered.

Furthermore, in addition to their structural

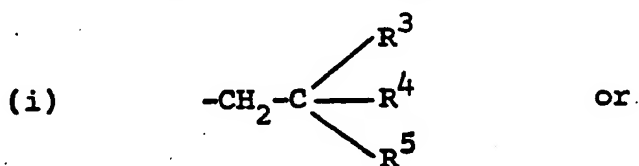
differences from known PGD compounds, the novel compounds of the present invention have an effect which has not hitherto been found in the known 9-deoxy- Δ^9 -PGD analogues that is, an anti-tumour effect. The above-described United States Patent specifications describe only the pharmacological properties known with the natural prostaglandins and none of the applications refers to an anti-tumour effect.

Accordingly, the present invention relates to prostaglandin D derivatives of the general formula:



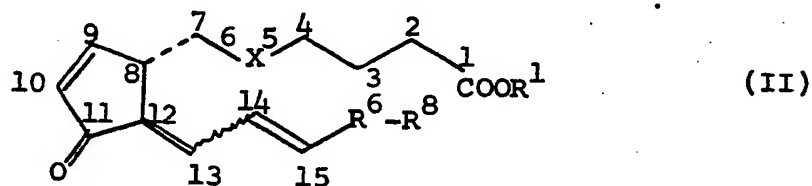
wherein R^1 represents a hydrogen atom or a straight-chain or branched-chain alkyl group of 1 - 12 carbon atoms, R^2 represents a group of the general formula:

15



wherein R^3 represents a straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms, R^4 represents a hydrogen

atom or a straight-chain or branched-chain alkyl group of
1 - 4 carbon atoms, R^5 represents a straight-chain or
branched-chain alkyl group of 1 - 10 carbon atoms, R^6
represents a single bond or a straight-chain or branched-
5 chain alkylene group of 1 - 5 carbon atoms, and R^7 represents
a cycloalkyl group of 4 - 7 carbon atoms either
unsubstituted or substituted by at least one straight-chain
or branched-chain alkyl group of 1 - 8 carbon atoms, X
represents an ethylene group ($-\text{CH}_2\text{CH}_2-$) or a cis-vinylene
10 group (cis- $\text{CH}=\text{CH}-$), the double bond between $\text{C}_9 - \text{C}_{10}$ is Z,
and the double bond between $\text{C}_{13} - \text{C}_{14}$ is E, and of the
general formula:



wherein R^1 , R^6 and X are as hereinbefore defined, R^8
15 represents a straight-chain or branched-chain alkyl group
of 1 - 8 carbon atoms, a cycloalkyl group of 4 - 7 carbon
atoms either unsubstituted or substituted by at least one
straight-chain or branched-chain alkyl group of 1 - 8
carbon atoms or represents a phenyl group or phenoxy group
20 either unsubstituted or substituted by at least one
halogen atom, trifluoromethyl group or straight-chain or
branched-chain alkyl group of 1 - 4 carbon atoms, the

double bonds between $C_{12} - C_{13}$ and between $C_{14} - C_{15}$ which may be in the same or different configurations, are E, Z or a mixture thereof (i.e. EZ), and the double bond between $C_9 - C_{10}$ is Z, provided that when R^6 represents a single bond, R^8 does not represent a substituted or unsubstituted phenoxy group, and cyclodextrin clathrates of compounds of general formulae (I) and (II), and non-toxic salts of acids of general formulae (I) and (II) wherein R^1 represents a hydrogen atom.

10 In the compounds of the general formula (I), there are at least three asymmetric carbons (that is, carbon atoms at the 8-, 12- and 15-positions), and in the compounds of the general formula (II), there is at least one asymmetric carbon atom (the carbon atom at the 8-position).

15 Further asymmetric carbon atoms may occur in the groups represented by R^1 , R^2 , R^6 and R^8 . The presence of asymmetric carbon atoms leads to the existence of isomerism. It is to be understood that all isomers and mixtures thereof arising from the presence of asymmetric carbon

20 atoms are to be considered within the scope of formulae I and II.

In the general formulae (I) and (II), as the

alkyl group of 1 - 12 carbon atoms represented by R^1 , there may be mentioned methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl groups and isomers thereof; R^1 preferably represents a
5 hydrogen atom or an alkyl group of 1 - 4 carbon atoms, and more especially a hydrogen atom or a methyl or ethyl group.

In the general formula (I), as the alkyl group of 1 - 4 carbon atoms represented by R^3 and R^4 , there may be mentioned methyl, ethyl, propyl, butyl and isomers
10 thereof. R^3 is preferably a methyl or ethyl group (especially methyl), and R^4 is preferably a hydrogen atom.

In the general formula (I), as the alkyl group of 1 - 10 carbon atoms represented by R^5 , there may be
15 mentioned methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and isomers thereof. R^5 is preferably a propyl, butyl or pentyl group.

In the general formulae (I) and (II), as the alkylene group of 1 - 5 carbon atoms represented by R^6
20 there may be mentioned methylene, ethylene, trimethylene, tetramethylene, pentamethylene and isomers thereof. R^6 preferably represents a single bond or a methylene or ethylene group [in particular a single bond in formula (I) and a single bond and a methylene group in formula (II)].

25 In the general formulae (I) and (II), as the substituted or unsubstituted cycloalkyl group represented

by R^7 and R^8 respectively, there may be mentioned cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups substituted by one or more methyl, ethyl, propyl, 5 butyl, pentyl, hexyl, heptyl or octyl groups; cyclobutyl, cyclopentyl or cyclohexyl groups either unsubstituted or substituted by one methyl, ethyl, propyl or butyl group are preferred; alkyl-substituted cyclopentyl is especially preferred.

10 In the general formula (II), as the alkyl group of 1 - 8 carbon atoms represented by R^8 , there may be mentioned methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomers thereof; butyl, pentyl or hexyl groups either unsubstituted or substituted by one or 15 two methyl or ethyl groups are preferred; pentyl and hexyl unsubstituted or substituted by one or two methyl groups are especially preferred.

In the general formula (II), as the substituted or unsubstituted phenyl or phenoxy group represented by R^8 , 20 there may be mentioned phenyl and phenoxy groups, and phenyl and phenoxy groups substituted by one or more atoms or groups selected from fluorine and chlorine atoms, and trifluoromethyl, methyl, ethyl, propyl or butyl groups; phenyl or phenoxy groups either unsubstituted or 25 substituted by one chlorine atom, trifluoromethyl group, methyl group or ethyl group are preferred; chlorine is a

preferred substituent.

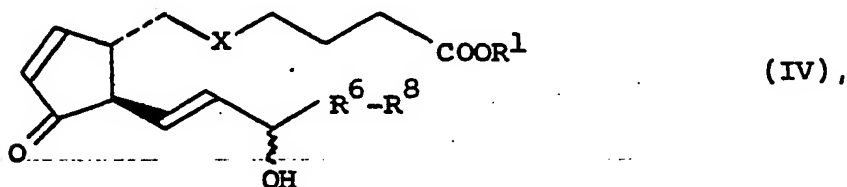
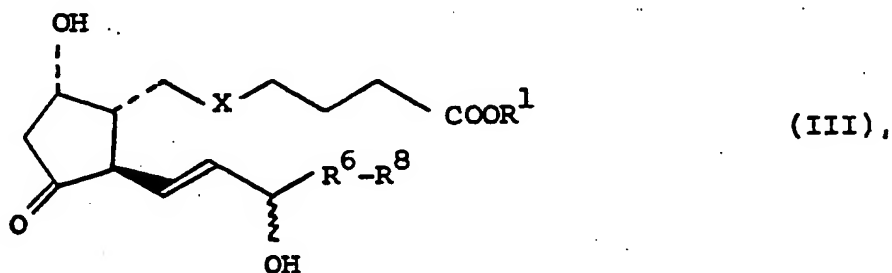
In the general formula (I), as a preferred R^2 , there may be mentioned 2-methylpentyl, 2-ethylpentyl, 2-methylhexyl, 2-ethylhexyl, 2-methylheptyl, and 2-ethylheptyl; and also cyclobutyl, 1-propylcyclobutyl, 1-butylcyclobutyl, 3-ethylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, cyclopentylmethyl, 2-cyclopentylethyl, 3-ethylcyclopentyl, 3-propylcyclopentyl, 3-butylcyclopentyl, cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, 4-methylcyclohexyl, 4-ethylcyclohexyl, 4-propylcyclohexyl and 4-butylcyclohexyl groups; 2-methylhexyl and 3-propylcyclopentyl are especially preferred.

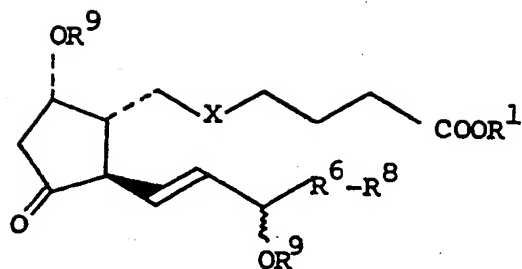
In the general formula (II), as a preferred $R^6 - R^8$, there may be mentioned butyl, pentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylpentyl, 1-ethylpentyl, 2-ethylpentyl, hexyl, 1-methylhexyl, 2-methylhexyl, 1-ethylhexyl, 2-ethylhexyl, heptyl, 2-methylheptyl, and 2-ethylheptyl; cyclobutyl, 1-propylcyclobutyl, 1-butylcyclobutyl, 3-ethylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, cyclopentylmethyl, 2-cyclopentylethyl, 3-ethylcyclopentyl, 3-propylcyclopentyl, 3-butylcyclopentyl, cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, 4-methylcyclohexyl, 4-ethylcyclohexyl, 4-propylcyclohexyl, and 4-butylcyclohexyl; and also benzyl, 2-phenylethyl, 4-methylbenzyl, 4-ethylbenzyl, phenoxymethyl, 2-phenoxyethyl, 3-chlorophenoxymethyl, 4-chlorophenoxymethyl,

3-trifluoromethylphenoxyethyl, 4-trifluoromethylphenoxy-
methyl, 4-methylphenoxyethyl and 4-ethylphenoxyethyl;
pentyl, 1,1-dimethylpentyl, 2-methylhexyl, 3-propylcyclo-
pentyl, benzyl and 3-chlorophenoxyethyl are especially
5 preferred.

Further, in the general formulae (I) and (II),
X is preferably a cis-vinylene group, and in the general
formula (I), the preferred configuration of the hydroxyl
group attached to the carbon atom at the 15-position is
10 the α -configuration.

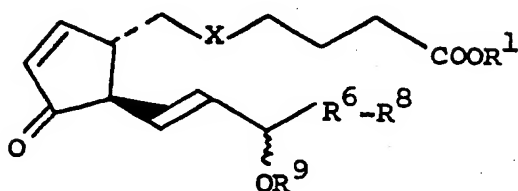
According to a feature of the present invention,
the prostaglandin derivatives of the general formula (II)
wherein the various symbols are as hereinbefore defined
may be prepared by reacting a compound of the general
15 formula:





(V)

or



(VI)

wherein X, R¹, R⁶ and R⁸ are as hereinbefore defined and R⁹ represents a tetrahydropyran-2-yl group, tetrahydrofuran-
 5 2-yl group either unsubstituted or substituted by at least one alkyl group, or a 1-ethoxyethyl group, preferably, a tetrahydropyran-2-yl group, with an aqueous acid, preferably in an inert organic solvent, for example, methylene chloride, chloroform, carbon tetrachloride,
 10 diethyl ether, N,N-dimethylformamide, tetrahydrofuran or a mixture of two or more such solvents, using as the aqueous acid, for example, an aqueous solution of an inorganic acid, eg hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid or an organic acid, e.g.

acetic acid, propionic acid or oxalic acid, at the reflux temperature of the solvent. The reaction is preferably carried out in tetrahydrofuran using 1 N hydrochloric acid at the reflux temperature of the reaction mixture.

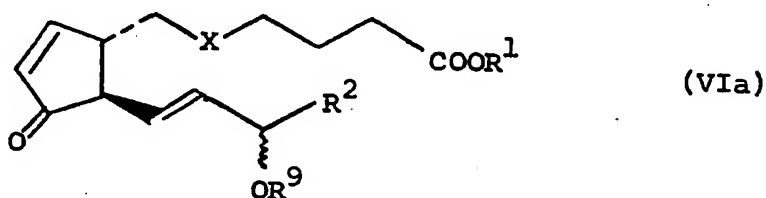
- 5 The prostaglandin derivatives of the general formulae (III) and (IV) wherein the various symbols are as hereinbefore defined may be prepared by hydrolyzing compounds of the general formulae (V) and (VI), respectively, under acidic conditions. This hydrolysis
- 10 may be conducted, for example:
- (1) in an aqueous solution of an organic acid such as acetic acid, propionic acid, oxalic acid or p-toluene-sulfonic acid or an aqueous solution of an inorganic acid such as hydrochloric acid, sulfuric acid or
 - 15 phosphoric acid, suitably in the presence of a water-miscible organic solvent, for example, a lower alkanol such as methanol or ethanol (preferably methanol) or an ether such as 1,2-dimethoxyethane, dioxan or tetrahydrofuran (preferably tetrahydrofuran)
 - 20 at a temperature of from room temperature to 80°C, or
 - (2) in an anhydrous lower alkanol such as methanol or ethanol in the presence of an organic acid such as p-toluenesulfonic acid or trifluoroacetic acid at a temperature of 10 - 45°C.

25 The hydrolysis is preferably conducted using a mixture of dilute hydrochloric acid and tetrahydrofuran, a

mixture of dilute hydrochloric acid and methanol, a mixture of acetic acid, water and tetrahydrofuran, a mixture of phosphoric acid, water and tetrahydrofuran, or a mixture of p-toluenesulfonic acid and anhydrous methanol.

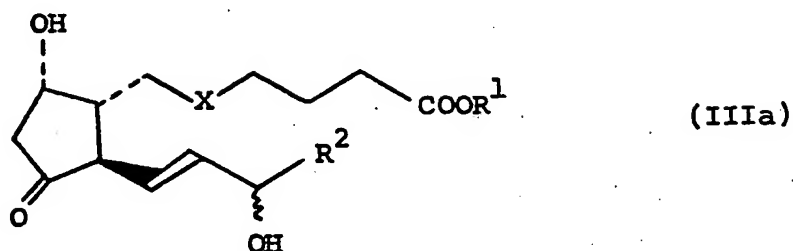
5 The prostaglandin derivatives of the general formula (IV) wherein the various symbols are as hereinbefore defined may also be prepared by subjecting a compound of the general formula (III) to a mild dehydration reaction, for example, by reaction with a tris hydrochloric acid
10 buffer solution at a temperature of 30 - 40°C.

The prostaglandin derivatives of the general formula (I) wherein the various symbols are as hereinbefore defined may be prepared by subjecting a compound of the general formula (VI) wherein the grouping $-R^6-R^8$ in the
15 general formula (VI) represents R^2 , i.e. a compound of the general formula:



(wherein the various symbols are as hereinbefore defined) to hydrolysis as hereinbefore described for the
20 conversion of compounds of general formulae (V) and (VI) to compounds of general formulae (III) and (IV), or by subjecting a compound of the general formula (III) wherein $-R^6-R^8$ in the general formula (III) represents R^2 ,

i.e. a compound of the general formula:



(wherein the various symbols are as hereinbefore defined)
to a mild dehydration reaction as hereinbefore described
5 for the conversion of compounds of general formula (III)
to compounds of general formula (IV).

According to a further feature of the present
invention, the esters of the general formulae (I), (II),
(III) and (IV) wherein R^1 represents a straight-chain or
10 branched-chain alkyl group of 1 - 12 carbon atoms and the
other symbols are as hereinbefore defined may also be
produced by esterifying the acids of the general formulae
(I), (II), (III) and (IV), respectively, wherein R^1
represents a hydrogen atom, and the other symbols are as
15 hereinbefore defined, by known methods.

By the expression "known methods" as used in
this specification and the accompanying claims is meant
methods heretofore used or described in the literature.

The esterification reaction may, for example, be
20 carried out by:

- (1) a process employing a diazoalkane, or
- (2) a process employing an N,N-dimethylformamide - dialkyl

acetal, or

- (3) a process employing a dicyclohexylcarbodiimide and an appropriate alcohol as described in Japanese Patent Specification No. 762305, or
- 5 (4) a process employing a pivaloyl halide and an appropriate alcohol as described in Japanese Patent Specification No. 756972, or
- (5) a process employing an arylsulfonyl halide or an alkylsulfonyl halide and an appropriate alcohol as
- 10 described in Japanese Patent Specification No. 759351.

The process employing a diazoalkane may be conducted by reaction with an appropriate diazoalkane in an inert organic solvent, for example, diethyl ether, ethyl acetate, methylene chloride, acetone or a mixture of

15 two or more such solvents, at from -10°C to room temperature, preferably at 0°C .

The process employing an N,N-dimethylformamide-dialkyl acetal may be conducted by reaction with an N,N-dimethylformamide - dialkyl acetal, for example, N,N-

20 dimethylformamide-dimethyl acetal, in anhydrous benzene at from 0°C to room temperature.

The process employing a dicyclohexylcarbodiimide may be conducted by reacting an appropriate acid and an appropriate alcohol in an inert organic solvent, for

25 example, a halogenated hydrocarbon such as chloroform or methylene chloride, in the presence of a base such as

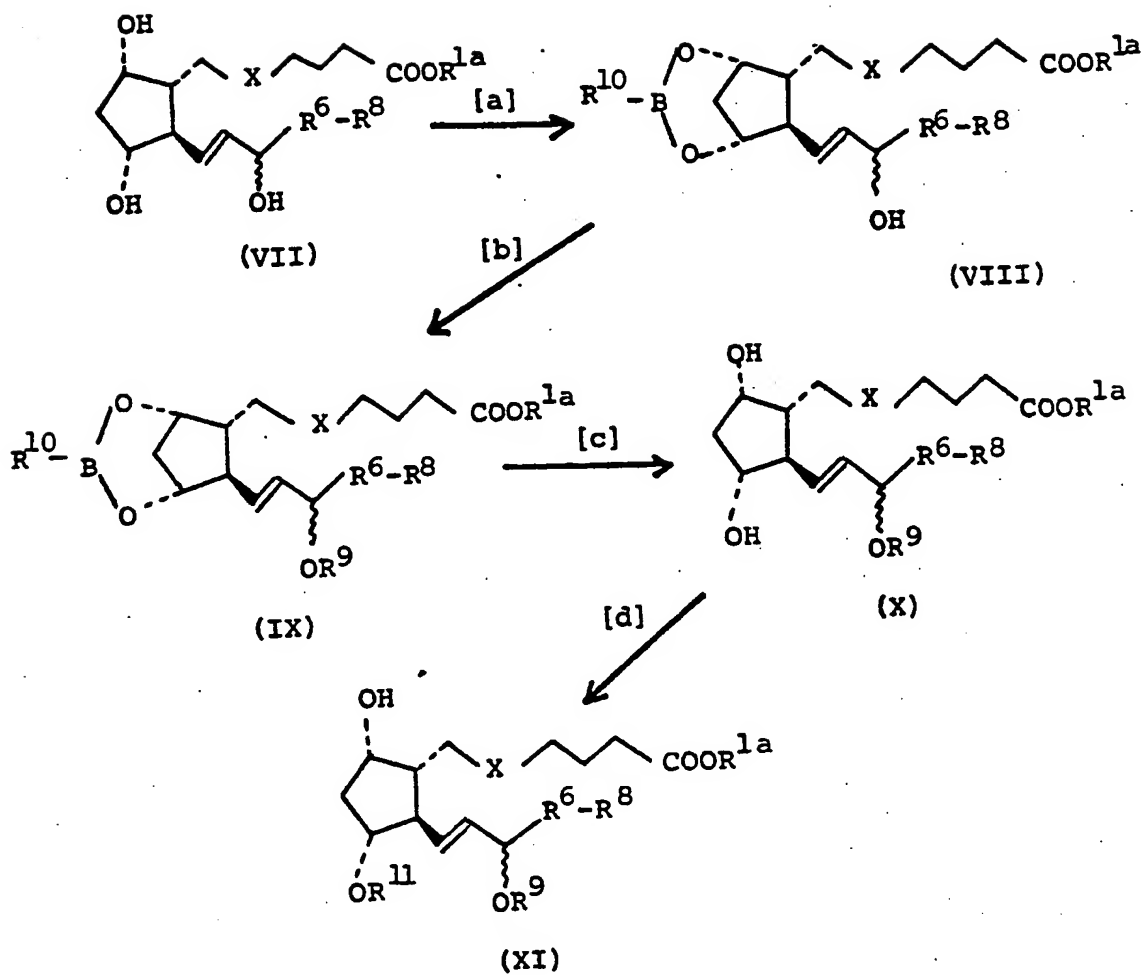
pyridine or picoline or, preferably, 4-dimethylamino-pyridine, at a temperature of 0°C to room temperature.

The process employing a pivaloyl halide, or an arylsulfonyl halide or an alkylsulfonyl halide may be
5 conducted by adding a tertiary amine such as triethylamine, or pyridine, and a pivaloyl halide, for example, pivaloyl chloride, or an arylsulfonyl halide, for example, benzenesulfonyl chloride or p-toluenesulfonyl chloride or an alkylsulfonyl halide, for example, methanesulfonyl
10 chloride or ethanesulfonyl chloride either in an inert organic solvent, for example, halogenated hydrocarbons such as chloroform or methylene chloride or diethyl ether or in the absence of a solvent to form a mixed acid anhydride, and subsequently adding the appropriate alcohol
15 and reacting at a temperature of 0°C to room temperature.

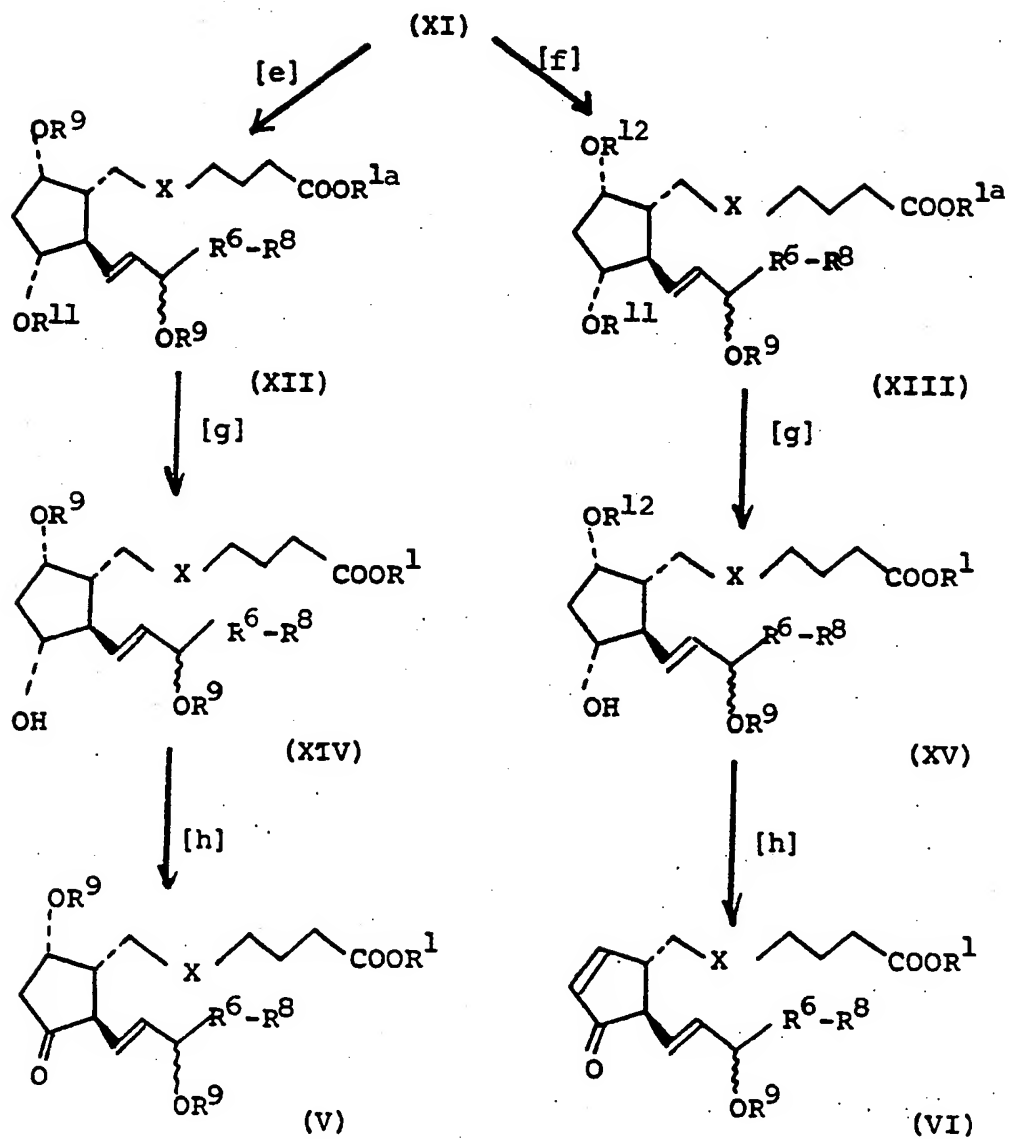
Starting materials of the general formulae (V) and (VI) may be prepared by the process described in the specifications of the United States Patent Nos. 3878239 (Derwent No. 76109U) and 4016184 (Derwent No. 24680Y),
20 and they may also be produced by the sequence of reaction steps illustrated in the following Scheme A. In Scheme A, R^{1a} represents a straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms, R^{10} represents a straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms or a phenyl group, preferably a n-butyl group or a phenyl group, R^{11} represents a straight-chain or branched-chain acyl group of 2—5 carbon atoms or a benzoyl group, preferably a benzoyl

group, or a tri-substituted silyl group such as a trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyl-dimethylsilyl, tribenzylsilyl or triphenylsilyl group, preferably a tert-butyldimethylsilyl group, R^{12} represents
5 an alkylsulfonyl group, or a substituted or unsubstituted arylsulfonyl group, preferably a mesyl group or a tosyl group, and the other symbols are as hereinbefore defined.

Scheme A



Scheme A (Continued)



All of the reaction steps in Scheme A may be conducted by known methods. For example, the step [a] may be conducted by reacting with a boric acid corresponding to R^{10} , for example, phenylboric acid [PhB(OH)₂] or butylboric acid [n-BuB(OH)₂], in an inert organic solvent such as methylene chloride, chloroform, carbon tetrachloride or tetrahydrofuran in the presence of molecular sieves 3A or 4A at reflux temperature [see J. C. S. Chem. Comm., page 658 (1975) and Prostaglandins, vol. 9, page 109 (1975)].

The step [b] may be conducted using, eg 2,3-dihydropyran, 2,3-dihydrofuran or ethyl vinyl ether in an inert organic solvent, for example, methylene chloride, chloroform or diethyl ether, in the presence of a condensing agent, for example, p-toluenesulfonic acid, sulfuric acid or trifluoroacetic acid at a temperature of from room temperature to -30°C. Preferably, it is conducted using 2,3-dihydropyran in methylene chloride in the presence of pyridine p-toluenesulfonate or p-toluenesulfonic acid at room temperature.

The step [c] may be conducted by reacting with an aqueous hydrogen peroxide solution in an aqueous solution of an alkanol of 1 - 4 carbon atoms, for example, aqueous methanol or aqueous ethanol, at a temperature of not higher than 60°C, preferably at 45 - 50°C.

The products of steps [a], [b] and [c] may be used without purification, in subsequent steps.

The step [d] may be conducted by selectively acylating or silylating the hydroxy group attached to the 11-position of the compound of the general formula (X). Such acylation may be conducted using an appropriate acyl chloride or acid anhydride, for example, benzoyl chloride, in an inert organic solvent, for example, methylene chloride, or in the absence of a solvent in the presence of a tertiary amine such as pyridine or triethylamine at a temperature not higher than room temperature, preferably at -30 to -40°C. A suitable silylation procedure is described in detail in "Protective Groups in Organic Synthesis" published by John Wiley & Sons, Inc. (USA), page 39 - 50 (1981) [referred to as "reference A" hereafter], and may be conducted by reacting with a chlorosilane compound of the general formula: Cl-R^{11a} , wherein R^{11a} represents a tri-substituted silyl group, in an inert organic solvent such as dimethylaminopyridine or dimethylformamide in the presence or a tertiary amine such as pyridine, imidazole or triethylamine at a temperature of from room temperature to 50°C.

The step [e] may be conducted as described for step [b].

The step [f] may be conducted by reacting with an alkylsulfonyl chloride such as mesyl chloride or an arylsulfonyl chloride such as tosyl chloride at a temperature of from -30°C to 50°C (i) in an inert organic solvent such as methylene chloride in the presence of a tertiary amine such as pyridine or triethylamine, or (ii) in pyridine.

The step [g] may be conducted by deacylation or desilylation. Such deacylation may be conducted by (1) using a hydroxide of an alkali metal such as lithium, sodium or potassium in an aqueous alkanol such as aqueous methanol or aqueous ethanol at a temperature of not lower than room temperature, preferably at 50 - 60°C, to give compounds of general formulae (XIV) and (XV) wherein R^1 represents a hydrogen atom, or (2) using anhydrous potassium carbonate in an anhydrous alkanol, such as anhydrous methanol, to give compounds of general formulae (XIV) and (XV) wherein R^1 represents an alkyl group of 1 to 4 carbon atoms. If desired, acids of the general formulae (XIV) and (XV) may be converted into the corresponding esters by the known esterification processes hereinbefore described. The desilylation above is described in detail in reference A and is preferably conducted by using tetrabutylammonium fluoride ($n\text{-Bu}_4\text{N}^+\text{F}^-$) in tetrahydrofuran at room temperature to give compounds of general formulae (XIV) and (XV) wherein R^1 represents an alkyl group of 1 - 4 carbon atoms.

If desired, esters of the general formulae (XIV) and (XV) may be converted into the corresponding acids by the method (1) described above for deacylation.

The step [h] is an oxidation reaction to convert the 11-hydroxy group in the compounds of general formulae (XIV) and (XV) into an oxo group and, in addition to eliminate the group OR¹² in the compound of general formula (XV) to from a double bond between C₉-C₁₀. Such an oxidation reaction is well known, and is described in detail in, 10 for example,

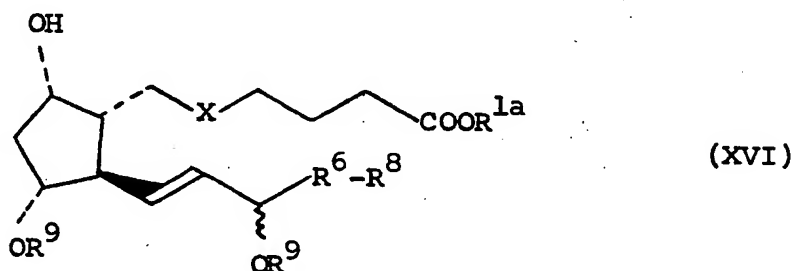
(a) "Synthetic Organic Chemistry III, Organic Synthesis 1", pp. 176-206 (compiled by Tetsuji Kameya and published by Nankodo (Japan) on Aug. 1, 1976) or

(b) "Compendium of Organic Synthetic Methods", vol. 1, vol. 2, and vol. 3, section 48 or 168 [published by John Wiley & Sons, Inc. (USA) in 1971, 1974, and 1977, respectively].

5 The oxidation is preferably carried out under mild neutral conditions using, for example, dimethylsulphide-N-chlorosuccinimide complex, thioanisole-N-chlorosuccinimide complex, dimethylsulphide-chlorine complex, thioanisole-chlorine complex [see J. Amer. Chem. Soc., 94, 7586 (1972) with respect to these complexes], dicyclohexylcarbodiimide-dimethylsulphoxide complex [see J. Amer. Chem. Soc., 87, 5661 (1965)], pyridinium chlorochromate ($C_5H_5NHCrO_3Cl$) [see Tetrahedron Letters, 2647 (1975)]; sulphuric anhydride-pyridine complex [see 15 J. Amer. Chem. Soc., 89, 5505 (1967)], chromyl chloride [see J. Amer. Chem. Soc., 97, 5929 (1975)], chromium trioxide-pyridine complex (for example, Collins' reagent), Jones' reagent or chromic acid solution (prepared from chromium trioxide, manganese sulfate, sulfuric acid and 20 water), or oxalyl chloride and dimethylsulfoxide (i.e. Swern oxidation); suitably the Collins oxidation, Jones oxidation or Swern oxidation may be employed. The Collins oxidation may be conducted in a halogenated hydrocarbon such as chloroform, methylene chloride or carbon 25 tetrachloride at a temperature of from room temperature to 0°C, preferably at 0°C. The Jones oxidation is generally

conducted at a temperature of not higher than room temperature. The Swern oxidation may be conducted by reaction in a halogenated hydrocarbon such as chloroform or methylene chloride at a temperature of from -50°C to 5 -60°C, and then treatment with triethylamine.

In the sequence of the reaction steps illustrated by the above Scheme A, the compounds of the general formula (VII) employed as the starting material are known per se as PGF derivatives, and may be produced by 10 converting the OR⁹ groups at the 11-position and the 15-position of a compound of the general formula:



(wherein the various symbols are as hereinbefore defined) to hydroxy groups by the hydrolysis under acidic conditions 15 hereinbefore described for the conversion of compounds of general formula (V) to those of general formula (III).

Compounds of general formula (XVI) can be obtained by the methods described in the following literature references and patent specifications, or obvious 20 modifications thereof:-

- (1) when the group -R⁶-R⁸ represents a pentyl group, as described in J. Amer. Chem. Soc., 91, 5675 (1969) or ibid., 92, 397 (1970);

- (2) when the group $-R^6-R^8$ represents an alkyl group, as described in Japanese Patent Kokai Nos. 42675/72, 54068/73, 64073/73, 124048/74, 95250/75, 96543/75 and 101340/75, British Patent Specification Nos. 1398291, 5 1483240 and 1540427, United States Patent Specification No. 4024174, and Belgian Patent No. 850084;
- (3) when R^8 of the group $-R^6-R^8$ represents a cycloalkyl group, as described in Japanese Patent Kokai Nos. 10 109353/74, 95250/75, 96543/75, 123647/75, 148339/75, 122040/76, 125256/76, 27753/77 and 25544/78, British Patent Specification Nos. 1464916, 1488141, 1483240, 1484210 and 1545213, United States Patent Specifications Nos. 3966792, 4034003, 4024174, 4045468 and 4087620, 15 and Belgian Patent No. 844256;
- (4) when R^8 of the group $-R^6-R^8$ represents a phenyl group or a phenoxy group, as described in Japanese Patent Kokai Nos. 95250/75, 96543/75, 59841/76, 101961/76 and 25745/77, British Patent Specifications 20 Nos. 1483240 and 1521747, United States Patent Specification Nos. 4024174 and 4065632, and Belgian Patent No. 845348.

Cyclodextrin clathrates of the compounds of general formulae (I) and (II) can be prepared by dissolving the 25 cyclodextrin in water or a water-miscible organic solvent, and adding to the solution the prostaglandin

derivative in a water-miscible organic solvent. The mixture is then heated and the desired cyclodextrin clathrate is isolated from the resulting solution by concentrating the mixture under reduced pressure, or
5 by cooling and separating the product by filtration or decantation. The ratio of organic solvent to water may be varied according to the solubilities of the starting materials and products. Preferably, the temperature is not allowed to exceed 70°C during preparation of the
10 cyclodextrin clathrate. α -, β - or γ -Cyclodextrin, or mixtures thereof, may be used to prepare the cyclodextrin clathrates. Conversion into cyclodextrin clathrates serves to increase the stability of the prostaglandin derivatives of the general formulae (I) and (II).

15 The prostaglandin derivatives of general formula (I) or (II) wherein R^1 represents a hydrogen atom may, if desired, be converted by known methods into salts. Preferably the salts are non-toxic salts. By the term "non-toxic salts",
20 as used in this specification, is meant salts the cations of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmacological properties of the compounds of general formula (I) or (II) are not vitiated by side-effects ascribable
25 to those cations. Preferably the salts are water-soluble. Suitable non-toxic salts include the alkali metal, e.g.

sodium or potassium, salts, the alkaline earth metal, e.g. calcium or magnesium, salts and ammonium salts, and pharmaceutically acceptable, (i.e. non-toxic) amine salts. Amines suitable for forming such salts with a carboxylic acid are well known and include, for example, amines derived in theory by the replacement of one or more of the hydrogen atoms of ammonia by groups, which may be the same or different when more than one hydrogen atom is replaced, selected from, for example, alkyl groups containing from 1 to 6 carbon atoms and hydroxyalkyl groups containing 2 or 3 carbon atoms. Suitable non-toxic amine salts are, e.g., tetraalkylammonium, such as tetramethylammonium, salts, and other organic amine salts such as methylamine salts, ethylamine salts, isopropylamine salts, tert-butylamine salts, dimethylamine salts, cyclopentylamine salts, benzylamine salts, phenethylamine salts, piperidine salts, monoethanolamine salts, diethanolamine salts, lysine salts or arginine salts.

Salts may be prepared from the acids of general formula (I) or (II) wherein R^1 represents a hydrogen atom, by known methods, for example by reaction of stoichiometric quantities of an acid of general formula (I) or (II) and the appropriate base, e.g. an alkali metal or alkaline earth metal hydroxide or carbonate, ammonium hydroxide, ammonia or an organic amine, in a suitable solvent. The salts

may be isolated by lyophilisation of the solution or, if sufficiently insoluble in the reaction medium, by filtration, if necessary, after removal of part of the solvent.

5 The prostaglandin D derivatives of the general formula (I) or (II), and cyclodextrin clathrates thereof, and non-toxic salts of the acids when R^1 in the general formulae (I) and (II) represents a hydrogen atom either do not show the pharmacological effects typical of other
10 prostaglandins, for example, hypotensive activity, inhibition of platelet aggregation, stimulation of uterine muscles and the production of diarrhoea or these effects are very weak. In contrast the anti-tumour effect of the derivatives of general formula (I) and (II) is extremely
15 strong and moreover their toxicity is extremely low. They may therefore be employed as very effective anti-tumour agents in the prevention or therapy of leukemia and solid cancer, and in treatment to produce remission thereof.

 In a laboratory, in vitro test on the inhibition
20 of proliferation of human myelogenous leukemic cells (HL-60) (the experimental method being described in detail below), the compound of the present invention, (5Z,9Z,14EZ)-11-oxoprostano-5,9,12,14-tetraenoic acid [produced in Example 2 (d)] inhibited the proliferation of the leukemic cells by
25 93.2% at a concentration of 5 μ g/ml. In contrast, PGD_2 (which is known to exert an anti-tumour effect) inhibited

the proliferation of the leukemic cells by only 55.6% at a concentration of 5 $\mu\text{g/ml}$ in the same test.

The test on the inhibition of the proliferation of human myelogenous leukemic cells was conducted by a well known method. The human myelogenous leukemic cells (HL-60) were added to an RPMI culture solution containing 10% bovine fetal serum, the number of cells in the culture solution was adjusted to 1×10^5 cells/ml, a solution in ethanol of the compound under test was added to give a concentration of 5 $\mu\text{g/ml}$, and the mixture was subjected to stationary culture at 37°C for 4 days. As a control, a culture solution containing 0.1% of ethanol was similarly cultured. The culture solutions were stained by the Trypan Blue staining method and the surviving cell number was measured to determine the degree of inhibition relative to the control. The results are given in the following Table.

Table: Inhibition of Proliferation Using Human Myelogenous Leukemic Cells

20	Compound	Surviving Cell Number (cells/ml)	Degree of Inhibition
	Control	44.0×10^4	-
25	(5Z,9Z,14EZ)-11-Oxoprostanoic Acid (Compound of the Invention)	3×10^4	93.2
	PGD ₂ (Known Compound)	19.5×10^4	55.6

With regard to the pharmacological effects typical of other prostaglandins, for example, in the intravenous administration to the allobarbitol-anesthetized dog, (5Z,9Z,14EZ)-11-oxoprostanoic acid
5 did not cause blood pressure depression at a dosage of 100 µg/kg animal body weight, whereas PGD₂ caused blood pressure depression by 26 mm Hg at a dosage of 10 µg/kg animal body weight and its effect lasted for 6 minutes.

The acute toxicity of the compounds of the
10 present invention was >50 mg/kg by intraperitoneal administration, so that the prostaglandin D derivatives of the present invention may be considered to be sufficiently safe and suitable for medical use. For example, the LD₅₀ value for (5Z,9Z,14EZ)-11-oxoprostanoic acid was 78 mg/kg by intraperitoneal administration in mice.

Preferred compounds of the general formula (I) of the present invention are, for example, as follows:

- 17-methyl-9-deoxy- Δ^9 -PGD₂,
- 17-ethyl-9-deoxy- Δ^9 -PGD₂,
- 5 17,20-dimethyl-9-deoxy- Δ^9 -PGD₂,
- 17-ethyl-20-methyl-9-deoxy- Δ^9 -PGD₂,
- 17-methyl-20-ethyl-9-deoxy- Δ^9 -PGD₂,
- 17,20-diethyl-9-deoxy- Δ^9 -PGD₂,
- 15-cyclobutyl-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,
- 10 15-(1-propylcyclobutyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,
- 15-(1-butylcyclobutyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,
- 15-(3-ethylcyclobutyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,
- 15 15-(3-propylcyclobutyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,
- 15-cyclopentyl-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,
- 16-cyclopentyl-17,18,19,20-tetranol-9-deoxy- Δ^9 -PGD₂,
- 20 17-cyclopentyl-18,19,20-trinor-9-deoxy- Δ^9 -PGD₂,
- 15-(3-ethylcyclopentyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,
- 15-(3-propylcyclopentyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,
- 25 15-(3-butylcyclopentyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,

- 15-cyclohexyl-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -PGD₂,
 16-cyclohexyl-17,18,19,20-tetranor-9-deoxy- Δ^9 -PGD₂,
 17-cyclohexyl-18,19,20-trinor-9-deoxy- Δ^9 -PGD₂,
 15-(4-methylcyclohexyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -
 5 PGD₂,
 15-(4-ethylcyclohexyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -
 PGD₂,
 15-(4-propylcyclohexyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -
 PGD₂,
 10 15-(4-butylcyclohexyl)-16,17,18,19,20-pentanol-9-deoxy- Δ^9 -
 PGD₂,
 and the corresponding methyl and ethyl esters, and the
 corresponding 9-deoxy- Δ^9 -PGD₁ analogues i.e. compounds of
 the general formula (I) wherein X represents an ethylene
 15 group .

- Preferred compounds of the general formula (II) of
 the present invention are, for example, as follows:
 (5Z,9Z,14EZ)-11-oxo-20-norprosta-5,9,12,14-tetraenoic acid,
 (5Z,9Z,14EZ)-11-oxo-prosta-5,9,12,14-tetraenoic acid,
 20 (5Z,9Z,14EZ)-11-oxo-16-methylprosta-5,9,12,14-tetraenoic
 acid,
 (5Z,9Z,14EZ)-11-oxo-17-methylprosta-5,9,12,14-tetraenoic
 acid,
 (5Z,9Z,14EZ)-11-oxo-18-methylprosta-5,9,12,14-tetraenoic
 25 acid,

- (5Z,9Z,14EZ)-11-oxo-16,16-dimethylprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-16-ethylprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-17-ethylprosta-5,9,12,14-tetraenoic acid,
- 5 (5Z,9Z,14EZ)-11-oxo-20-methylprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-16,20-dimethylprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-17,20-dimethylprosta-5,9,12,14-tetraenoic
- 10 acid,
- (5Z,9Z,14EZ)-11-oxo-16-ethyl-20-methylprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-17-ethyl-20-methylprosta-5,9,12,14-tetraenoic acid,
- 15 (5Z,9Z,14EZ)-11-oxo-20-ethylprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-17-methyl-20-ethylprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-17,20-diethylprosta-5,9,12,14-tetraenoic acid,
- 20 (5Z,9Z,14EZ)-11-oxo-15-cyclobutyl-16,17,18,19,20-pentanorprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-15-(1-propylcyclobutyl)-16,17,18,19,20-pentanorprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-15-(1-butylcyclobutyl)-16,17,18,19,20-
- 25 pentanorprosta-5,9,12,14-tetraenoic acid,
- (5Z,9Z,14EZ)-11-oxo-15-(3-ethylcyclobutyl)-16,17,18,19,20-
-

- pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-15-(3-propylcyclobutyl)-16,17,18,19,20-
pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-15-cyclopentyl-16,17,18,19,20-
- 5 pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-cyclopentyl-17,18,19,20-
tetranorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-17-cyclopentyl-18,19,20-trinorprosta-
5,9,12,14-tetraenoic acid,
- 10 (5Z,9Z,14EZ)-11-oxo-15-(3-ethylcyclopentyl)-16,17,18,19,20-
pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-15-(3-propylcyclopentyl)-16,17,18,19,20-
pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-15-(3-butylcyclopentyl)-16,17,18,19,20-
- 15 pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-15-cyclohexyl-16,17,18,19,20-
pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-cyclohexyl-17,18,19,20-tetranorprosta-
5,9,12,14-tetraenoic acid,
- 20 (5Z,9Z,14EZ)-11-oxo-17-cyclohexyl-18,19,20-trinorprosta-
5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-15-(4-methylcyclohexyl)-16,17,18,19,20-
pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-15-(4-ethylcyclohexyl)-16,17,18,19,20-
- 25 pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-15-(4-propylcyclohexyl)-16,17,18,19,20-
-

- pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-15-(4-butylcyclohexyl)-16,17,18,19,20-
pentanorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-phenyl-17,18,19,20-tetranorprosta-
5 5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-17-phenyl-18,19,20-trinorprosta-
5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-(4-methylphenyl)-17,18,19,20-
tetranorprosta-5,9,12,14-tetraenoic acid,
10 (5Z,9Z,14EZ)-11-oxo-16-(4-ethylphenyl)-17,18,19,20-
tetranorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-phenoxy-17,18,19,20-tetranorprosta-
5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-17-phenoxy-18,19,20-trinorprosta-
15 5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-(3-chlorophenoxy)-17,18,19,20-
tetranorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-(4-chlorophenoxy)-17,18,19,20-
tetranorprosta-5,9,12,14-tetraenoic acid,
20 (5Z,9Z,14EZ)-11-oxo-16-(3-trifluoromethylphenoxy)-
17,18,19,20-tetranorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-(4-trifluoromethylphenoxy)-
17,18,19,20-tetranorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-(4-methylphenoxy)-17,18,19,20-
25 tetranorprosta-5,9,12,14-tetraenoic acid,
(5Z,9Z,14EZ)-11-oxo-16-(4-ethylphenoxy)-17,18,19,20-
-

tetranorprosta-5,9,12,14-tetraenoic acid,
and the corresponding methyl and ethyl esters, and the
corresponding compounds wherein X represents an ethylene
group.

The following Reference Examples and Examples illustrate the preparation of compounds of the present invention. In the Reference Examples and Examples, 'TLC', 'NMR', 'IR' and 'Mass' represent 'Thin layer chromatography', 'Nuclear magnetic resonance spectrum', 'Infrared absorption spectrum' and 'Mass spectrum', respectively. The solvents in parentheses specified in chromatographic separations show the developing solvents used : ratios are by volume. Except when specified otherwise, infrared absorption spectra were recorded by the liquid film method and nuclear magnetic resonance spectra were recorded in deuteriochloroform (CDCl_3) solution.

Reference Example 1

(5Z,13E)-(9 α ,11 α ,15S,17S)-9,11-dihydroxy-15-(tetrahydropyran-2-yloxy)-17,20-dimethylprosta-5,13-dienoic acid methyl ester.

To a mixture of 1.1 g of 17S,20-dimethyl-PGF_{2 α} methyl ester in 25 ml of dry methylene chloride, and 409 mg of phenylboric acid, was added a molecular sieve 4A (20 - 25 grains) and the mixture obtained was refluxed for one hour. After cooling to room temperature, the reaction mixture was filtered and to the filtrate obtained were added 0.382 ml of 2,3-dihydropyran and 70.3 mg of pyridine p-toluenesulfonate and then the mixture was stirred overnight. To the reaction mixture was added 90 ml of ethyl acetate and the mixture was washed successively with a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride,

dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue obtained was dissolved in 10 ml of methanol and thereto were added 40 ml of water and 4.0 ml of a 30% aqueous solution of hydrogen peroxide and the solution was warmed to 45 - 48°C. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure; to the residue obtained was added 50 ml of ethyl acetate and then the solution obtained was washed successively with water and a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:cyclohexane=1:1) to give 920 mg of the title compound having the following physical characteristics:

15 TLC (benzene:ethyl acetate=1:2): $R_f=0.43$;
NMR: $\delta=5.7-5.2$ (4H, m), 4.7 (1H, m), 3.6 (3H, s), 4.2-3.3 (5H, m), 1.0-0.8 (6H, m);
IR: $\nu=3440, 2938, 1737 \text{ cm}^{-1}$;
Mass: $m/e=462$.

20 By the same procedure as described in Reference Example 1, the following compounds were prepared.

(a) (5Z,13E)-(9 α ,11 α ,15S)-9,11-dihydroxy-15-(tetrahydropyran-2-yloxy)-15-(3-propylcyclopentyl)-16,17,18,19,20-pentanorprosta-5,13-dienoic acid methyl ester

25

Starting material: 15-(3-propylcyclopentyl)-16,17,18,19,20-

pentanor-PGF_{2α} methyl ester;

TLC (benzene:ethyl acetate=1:2): Rf=0.45;

NMR: δ=5.7-5.2 (4H, m), 4.7 (1H, m), 3.7 (3H, s), 4.2-3.3 (5H, m), 0.9 (3H, t);

5 IR: ν=3440, 2935, 1735 cm⁻¹;

Mass: m/e=474.

(b) (5Z,13E)-(9α,11α,15S)-9,11-dihydroxy-15-(tetrahydropyran-2-yloxy)-16-phenyl-17,18,19,20-tetranorprosta-5,13-dienoic acid methyl ester

10 Starting material: 16-phenyl-17,18,19,20-tetranor-PGF_{2α} methyl ester;

TLC (benzene:ethyl acetate=1:2): Rf=0.40;

NMR: δ=7.5-7.1 (5H, m), 5.7-5.2 (4H, m), 4.7 (1H, m), 3.6 (3H, s), 4.2-3.3 (5H, m);

15 IR: ν=3350, 2937, 1737 cm⁻¹;

Mass: m/e=454.

(c) (5Z,13E)-(9α,11α,15R)-9,11-dihydroxy-15-(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-17,18,19,20-tetranorprosta-5,13-dienoic acid methyl ester

20

Starting material: 16-(3-chlorophenoxy)-17,18,19,20-tetranor-PGF_{2α} methyl ester;

TLC (benzene:ethyl acetate=1:2): Rf=0.40;

NMR: δ=7.3-6.7 (4H, m), 5.7-5.2 (4H, m), 4.7-3.8 (8H, m), 3.7 (3H, s);

25

IR: ν=3440, 2935, 1737, 1600 cm⁻¹;

Mass: m/e=504.

(d) (5Z,13E)-(9 α ,11 α ,15R)-9,11-dihydroxy-15-(tetrahydropyran-2-yloxy)-16,16-dimethylprosta-5,13-dienoic acid methyl ester

5 Starting material: 16,16-dimethyl-PGF_{2 α} methyl ester;

TLC (ethyl acetate): Rf=0.65;

NMR: δ =5.7-5.1 (4H, m), 4.6 (1H, m), 3.6 (3H, s), 1.0-0.8 (9H, m);

IR: ν =3440, 2940, 1740, 1440 cm⁻¹.

10 Reference Example 2

(5Z,13E)-(9 α ,11 α ,15S,17S)-9-hydroxy-11-benzoyloxy-15-(tetrahydropyran-2-yloxy)-17,20-dimethylprosta-5,13-dienoic acid methyl ester.

To a solution of 970 mg of the 9,11-dihydroxy
15 compound (prepared in Reference Example 1) in 40 ml of methylene chloride, was added 1.63 ml of pyridine and the solution was cooled to -30 to -40°C. To the solution was added dropwise slowly 0.71 ml of benzoyl chloride in 3 ml of methylene chloride and the solution was stirred for 20
20 minutes at the same temperature. After adding 12.1 ml of methanol, the solution was further stirred for 20 minutes and warmed to 0°C. To the reaction mixture was added 20 ml of methylene chloride and the mixture was washed successively with water and a saturated aqueous solution of sodium chloride,

dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate:cyclohexane=3:1) to give 950 mg of the title compound having the following physical characteristics:

TLC (cyclohexane:ethyl acetate=2:1): $R_f=0.48$;

NMR: $\delta=8.1-7.8$ (2H, m), $7.6-7.2$ (3H, m), $5.8-5.2$ (4H, m), $5.2-4.9$ (1H, m), 4.5 (1H, m), 3.6 (3H, s), $1.0-0.8$ (6H, m);

IR: $\nu=3530, 2940, 1737, 1720, 1275 \text{ cm}^{-1}$.

By the same procedure as described in Reference Example 2, the following compounds were prepared.

- (a) (5Z,13E)-(9 α ,11 α ,15S)-9-hydroxy-11-benzoyloxy-15-(tetrahydropyran-2-yloxy)-15-(3-propylcyclopentyl)-
16,17,18,19,20-pentanorprosta-5,13-dienoic acid
methyl ester

Starting material: the 9,11-dihydroxy compound prepared in Reference Example 1(a);

TLC (cyclohexane:ethyl acetate=2:1): $R_f=0.50$;

NMR: $\delta=8.1-7.8$ (2H, m), $7.6-7.2$ (3H, m), $5.8-5.2$ (4H, m), $5.2-4.9$ (1H, m), 4.6 (1H, m), 3.6 (3H, s), 0.9 (3H, t);

IR: $\nu=3530, 2935, 1735, 1720 \text{ cm}^{-1}$.

- (b) (5Z,13E)-(9 α ,11 α ,15S)-9-hydroxy-11-benzoyloxy-15-(tetrahydropyran-2-yloxy)-16-phenyl-17,18,19,20-tetranorprosta-5,13-dienoic acid methyl ester

Starting material: the 9,11-dihydroxy compound prepared in

Reference Example 1(b);

TLC (cyclohexane:ethyl acetate=2:1): $R_f=0.45$;

NMR: $\delta=8.1-7.1$ (10H, m), $5.8-5.2$ (4H, m), $5.2-4.9$ (1H, m),

5 4.6 (1H, m), 3.6 (3H, s);

IR: $\nu=3540, 2935, 1737, 1720 \text{ cm}^{-1}$.

(c) (5Z,13E)-(9 α ,11 α ,15R)-9-hydroxy-11-benzoyloxy-15-
 (tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-
 17,18,19,20-tetranorprosta-5,13-dienoic acid methyl
10 ester

Starting material: the 9,11-dihydroxy compound prepared in

Reference Example 1(c);

TLC (cyclohexane:ethyl acetate=2:1): $R_f=0.45$;

NMR: $\delta=8.1-7.8$ (2H, m), $7.6-6.7$ (7H, m), $5.8-5.2$ (4H, m),

15 $5.2-4.9$ (1H, m), 3.7 (3H, s);

IR: $\nu=3530, 2935, 1736, 1720, 1600, 1273 \text{ cm}^{-1}$.

(d) (5Z,13E)-(9 α ,11 α ,15R)-9-hydroxy-11-benzoyloxy-15-
 (tetrahydropyran-2-yloxy)-16,16-dimethylprosta-
 5,13-dienoic acid methyl ester

20 Starting material: the 9,11-dihydroxy compound prepared in

Reference Example 1(d);

TLC (cyclohexane:ethyl acetate=2:1): $R_f=0.49$;

NMR: $\delta=8.1-7.8$ (2H, m), $7.6-7.2$ (3H, m), $5.8-5.2$ (4H, m),

$5.2-4.9$ (1H, m), 4.5 (1H, m), 3.6 (3H, s), $1.0-0.8$

25 (9H, m).

Reference Example 3

(5Z,13E)-(9 α ,11 α ,15S,17S)-9,15-bis(tetrahydropyran-2-yloxy)-11-benzoyloxy-17,20-dimethylprosta-5,13-dienoic acid methyl ester.

5 To a solution of 4.5 g of the 9-hydroxy compound (prepared in Reference Example 2) in 20 ml of methylene chloride, was added dropwise one ml of 2,3-dihydropyran and then was added 10 mg of p-toluenesulfonic acid. After stirring for 15 minutes, 0.1 ml of triethylamine was added to
10 the reaction mixture and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: n-hexane:ethyl acetate=5:1) to give 4.0 g of the title compound having the following physical characteristics:

15 TLC (n-hexane:ethyl acetate=2:1): R_f=0.47;

NMR: δ =8.1-7.9 (2H, m), 7.6-7.2 (3H, m), 5.7-5.2 (4H, m),
5.2-4.9 (1H, m), 4.75-4.4 (2H, m), 3.7 (3H, s),
1.0-0.7 (6H, m);

IR: ν =2940, 1736, 1720 cm⁻¹.

20 By the same procedure as described in Reference Example 3, the following compounds were prepared.

(a) (5Z,13E)-(9 α ,11 α ,15S)-9,15-bis(tetrahydropyran-2-yloxy)-11-benzoyloxy-15-(3-propylcyclopentyl)-16,17,18,19,20-pentanorprosta-5,13-dienoic acid
25 methyl ester

Starting material: the 9-hydroxy compound prepared in

Reference Example 2(a);

TLC (n-hexane:ethyl acetate=2:1): R_f =0.49;

NMR: δ =8.1-7.9 (2H, m), 7.6-7.2 (3H, m), 5.7-5.2 (4H, m),
5.3-4.9 (1H, m), 4.8-4.4 (2H, m), 3.7 (3H, s), 0.89
(3H, t);

IR: ν =2940, 1735, 1722 cm^{-1} .

(b) (5Z,13E)-(9 α ,11 α ,15S)-9,15-bis(tetrahydropyran-2-
yloxy)-11-benzoyloxy-16-phenyl-17,18,19,20-
tetranorprosta-5,13-dienoic acid methyl ester

Starting material: the 9-hydroxy compound prepared in

Reference Example 2(b);

TLC (n-hexane:ethyl acetate=2:1): R_f =0.45;

NMR: δ =8.1-7.1 (10H, m), 5.7-5.2 (4H, m), 5.2-4.9 (1H, m),
4.7-4.5 (2H, m), 3.7 (3H, s);

IR: ν =2935, 1736, 1720 cm^{-1} .

(c) (5Z,13E)-(9 α ,11 α ,15R)-9,15-bis(tetrahydropyran-2-
yloxy)-11-benzoyloxy-16-(3-chlorophenoxy)-
17,18,19,20-tetranorprosta-5,13-dienoic acid methyl
ester

Starting material: the 9-hydroxy compound prepared in

Reference Example 2(c);

TLC (n-hexane:ethyl acetate=2:1): R_f =0.45;

NMR: δ =8.1-7.9 (2H, m), 7.6-6.7 (7H, m), 5.7-5.2 (4H, m),
5.2-4.9 (1H, m), 3.7 (3H, s);

IR: ν =2940, 1737, 1720, 1600 cm^{-1} .

(d) (5Z,13E)-(9 α ,11 α ,15R)-9,15-bis(tetrahydropyran-2-yloxy)-11-benzoyloxy-16,16-dimethylprosta-5,13-dienoic acid methyl ester

Starting material: the 9-hydroxy compound prepared in

5 Reference Example 2(d);

TLC (cyclohexane:ethyl acetate=2:1) : R_f=0.57;

NMR: δ =8.1-7.8 (2H, m), 7.6-7.2 (3H, m), 5.8-5.2 (4H, m),
5.2-4.9 (1H, m), 4.7-4.4 (2H, m), 3.6 (3H, s),
1.0-0.8 (9H, m).

10 Reference Example 4

(5Z,13E)-(9 α ,11 α ,15S,17S)-9,15-bis(tetrahydropyran-2-yloxy)-11-hydroxy-17,20-dimethylprosta-5,13-dienoic acid.

To a solution of 1.26 g of the 11-benzoyloxy compound (prepared in Reference Example 3) in 10 ml of
15 methanol, was added 3.8 ml of a 2N aqueous solution of potassium hydroxide, and the solution obtained was stirred for 3 hours at 50 - 60°C. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure until its volume was reduced to half, and then 50 ml of a 20%
20 aqueous solution of ammonium chloride was added thereto. The solution was extracted with 50 ml of ethyl acetate twice (total: 100 ml) and the extract was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to

give 1.04 g of the title compound as crude product having the following physical characteristics. The product obtained was used in the procedure of Reference Example 5 without purification.

5 TLC (benzene:ethyl acetate=2:1): Rf=0.07.

By the same procedure as described in Reference Example 4, the following compounds were prepared.

(a) (5Z,13E)-(9 α ,11 α ,15S)-9,15-bis(tetrahydropyran-2-yloxy)-11-hydroxy-15-(3-propylcyclopentyl)-
10 16,17,18,19,20-pentanoic acid

Starting material: the 11-benzoyloxy compound prepared in Reference Example 3(a);

TLC (benzene:ethyl acetate=2:1): Rf=0.07.

(b) (5Z,13E)-(9 α ,11 α ,15S)-9,15-bis(tetrahydropyran-2-yloxy)-11-hydroxy-16-phenyl-17,18,19,20-
15 tetranorprosta-5,13-dienoic acid

Starting material: the 11-benzoyloxy compound prepared in Reference Example 3(b);

TLC (benzene:ethyl acetate=2:1): Rf=0.08.

20 (c) (5Z,13E)-(9 α ,11 α ,15R)-9,15-bis(tetrahydropyran-2-yloxy)-11-hydroxy-16-(3-chlorophenoxy)-
17,18,19,20-tetranorprosta-5,13-dienoic acid

Starting material: the 11-benzoyloxy compound prepared in Reference Example 3(c);

25 TLC (benzene:ethyl acetate=2:1): Rf=0.06.

(d) (5Z,13E)-(9 α ,11 α ,15R)-9,15-bis(tetrahydropyran-2-yloxy)-11-hydroxy-16,16-dimethylprosta-5,13-dienoic

acid

Starting material: the 11-benzoyloxy compound prepared in

Reference Example 3(d);

TLC (cyclohexane:ethyl acetate=2:1): R_f =0.08;

1H NMR: δ =5.7-5.3 (4H, m), 4.7-4.5 (2H, m), 1.0-0.8 (9H, m);

Mass: m/e =448, 431, 367, 346.

Reference Example 5

(5Z,13E)-(9 α ,15S,17S)-11-oxo-9,15-bis(tetrahydropyran-2-yloxy)-17,20-dimethylprosta-5,13-dienoic acid.

- 10 A solution of 1.04 g of the 11-hydroxy compound (prepared in Reference Example 4) in 10 ml of acetone was cooled to -30°C and Jones reagent (prepared from 378 mg of chromium trioxide, 0.331 ml of concentrated sulfuric acid and 1.41 ml of water) was added thereto dropwise, and then
- 15 the solution was stirred for 30 minutes at the same temperature. After adding one ml of isopropyl alcohol and 100 ml of water, successively, the reaction mixture was extracted with 50 ml of diethyl ether three times (total: 150 ml) and the extract was washed successively with water and a
- 20 saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: cyclohexane:ethyl acetate=2:1) to give
-

652 mg of the title compound having the following physical characteristics:

TLC (benzene:ethyl acetate=1:2): R_f =0.71;

NMR: δ =10.1 (1H, s), 5.7-5.2 (4H, m), 4.8-4.5 (2H, m),

5 1.0-0.7 (6H, m);

Mass: m/e =464, 446.

By the same procedure as described in Reference Example 5, the following compounds were prepared.

(a) (5Z,13E)-(9 α ,15S)-11-oxo-9,15-bis(tetrahydropyran-
10 2-yloxy)-15-(3-propylcyclopentyl)-16,17,18,19,20-
pentanorprosta-5,13-dienoic acid

Starting material: the 11-hydroxy compound prepared in
Reference Example 4(a);

TLC (benzene:ethyl acetate=1:2): R_f =0.71;

15 NMR: δ =10.3 (1H, s), 5.7-5.2 (4H, m), 4.8-4.5 (2H, m), 0.88
(3H, t);

Mass: m/e =476, 458.

(b) (5Z,13E)-(9 α ,15S)-11-oxo-9,15-bis(tetrahydropyran-
2-yloxy)-16-phenyl-17,18,19,20-tetranorprosta-5,13-
20 dienoic acid

Starting material: the 11-hydroxy compound prepared in
Reference Example 4(b);

TLC (benzene:ethyl acetate=1:2): R_f =0.70;

NMR: δ =10.3 (1H, s), 7.5-7.1 (5H, m), 5.7-5.2 (4H, m),
25 4.8-4.5 (2H, m);

Mass: m/e =456, 438.

(c) (5Z,13E)-(9 α ,15R)-11-oxo-9,15-bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-17,18,19,20-tetranorprosta-5,13-dienoic acid

Starting material: the 11-hydroxy compound prepared in

5 Reference Example 4(c);

TLC (benzene:ethyl acetate=1:2): R_f=0.70;

NMR: δ =10.3 (1H, s), 7.3-6.7 (4H, m), 5.7-5.2 (4H, m);

Mass: m/e=506, 488.

(d) (5Z,13E)-(9 α ,15R)-11-oxo-9,15-bis(tetrahydropyran-2-yloxy)-16,16-dimethylprosta-5,13-dienoic acid

10

Starting material: the 11-hydroxy compound prepared in

Reference Example 4(d);

TLC (cyclohexane:ethyl acetate=1:1): R_f=0.44;

NMR: δ =5.78-5.30 (4H, m), 4.85-3.35 (8H, m), 1.00-0.80

15 (9H, m);

IR: ν =2930, 1735, 1700 cm⁻¹;

Mass: m/e=447, 365, 345.

Reference Example 6

(5Z,13E)-(9 α ,15S,17S)-11-oxo-9,15-dihydroxy-17,20-dimethylprosta-5,13-dienoic acid (i.e. 17S,20-dimethyl-PGD₂)

20

A mixture of 600 mg of the 11,15-

bis(tetrahydropyran-2-yloxy) compound (prepared in Reference Example 5), 1.15 ml of tetrahydrofuran and 10 ml of a 65% (v/v) aqueous solution of acetic acid was stirred for 8 minutes at

TLC (chloroform:tetrahydrofuran:acetic acid=20:4:1): Rf=0.38;
NMR: δ =5.74-5.36 (4H, m), 4.50 (1H, m), 4.12 (1H, m), 2.82
(1H, m), 1.02-0.81 (6H, m);
IR: ν =3420, 2920, 1740, 1710 cm^{-1} ;

By the same procedure as described in Reference Example 6, the following compounds were prepared.

Starting material: the 9,15-bis(tetrahydropyran-2-yloxy) compound prepared in Reference Example 5 (a);

25 TLC (chloroform:tetrahydrofuran:acetic acid=20:4:1): Rf=0.40;
NMR: δ =5.75-5.35 (4H, m), 4.55 (1H, m), 4.12 (1H, m), 2.80

(1H, m), 0.89 (3H, t);

IR: $\nu=3430, 2920, 1740, 1712 \text{ cm}^{-1}$;

Mass: $m/e=374, 356$.

(b) (5Z,13E)-(9 α ,15S)-11-oxo-9,15-dihydroxy-16-phenyl-
5 17,18,19,20-tetranorprosta-5,13-dienoic acid (i.e.
16-phenyl-17,18,19,20-tetranor-PGD₂)

Starting material: the 9,15-bis(tetrahydropyran-2-yloxy)
compound prepared in Reference Example
5(b);

10 TLC (chloroform:tetrahydrofuran:acetic acid=20:4:1): $R_f=0.38$;

NMR: $\delta=7.53-7.14$ (5H, m), $5.73-5.36$ (4H, m), 4.55 (1H, m),
 4.20 (1H, m), 2.85 (1H, m);

IR: $\nu=3420, 2920, 1742, 1711 \text{ cm}^{-1}$;

Mass: $m/e=354, 336$.

15 (c) (5Z,13E)-(9 α ,15R)-11-oxo-9,15-dihydroxy-16-(3-
chlorophenoxy)-17,18,19,20-tetranorprosta-5,13-
dienoic acid (i.e. 16-(3-chlorophenoxy)-
17,18,19,20-tetranor-PGD₂)

Starting material: the 9,15-bis(tetrahydropyran-2-yloxy)

20 compound prepared in Reference Example
5(c);

TLC (chloroform:tetrahydrofuran:acetic acid=20:4:1): $R_f=0.36$;

NMR: $\delta=7.28-6.70$ (4H, m), $5.75-5.35$ (4H, m), $4.63-4.35$
(2H, m), 3.94 (2H, d), 2.85 (1H, m);

25 IR: $\nu=3430, 2925, 1740, 1710, 1600 \text{ cm}^{-1}$;

Mass: $m/e=404, 386$.

(d) (5Z,13E)-(9 α ,15R)-11-oxo-9,15-dihydroxy-16,16-dimethylprosta-5,13-dienoic acid (i.e. 16,16-dimethyl-PGD₂)

Starting material: the 9,15-bis(tetrahydropyran-2-yloxy)
5 compound prepared in Reference Example
5(d);

TLC (chloroform:tetrahydrofuran:acetic acid=20:2:1): R_f=0.08;

NMR: δ =5.90-5.35 (4H, m), 4.60-4.45 (1H, m), 3.90 (1H, d),
2.85 (1H, dd), 1.00-0.90 (9H, m);

10 IR: ν =2955-2920, 1860, 1730-1695, 1450 cm⁻¹;

Mass: m/e=362, 344, 301, 268.

Reference Example 7

(5Z,13E)-(9 α ,15S)-11-oxo-9,15-dihydroxyprosta-5,13-dienoic
acid ethyl ester (i.e. PGD₂ ethyl ester)

15 Under an atmosphere of nitrogen, to a solution of
50 mg of PGD₂ (prepared by the method as described in Example
1 [B] in the specification of the Japanese Patent Kokoku
No. 54-32773) in 0.5 ml of ethanol was added 29 mg of
dicyclohexylcarbodiimide at 0°C, followed by 17 mg of
20 4-dimethylaminopyridine in 2.5 ml of methylene chloride
added slowly dropwise. After warming to room temperature,
the reaction mixture was stirred for 2 hours. The reaction
mixture was diluted with diethyl ether, washed with water,
dried and concentrated under reduced pressure. The residue

was purified by column chromatography on silica gel
(eluent: diethyl ether:n-hexane=1:1→diethyl ether only)
to give 16 mg of the title compound having the
following physical characteristics:

5 TLC (chloroform:tetrahydrofuran:acetic acid=10:2:1): $R_f=0.49$;

NMR: $\delta=5.72-5.38$ (4H, m), 4.52-4.40 (1H, m), 4.13 (2H, q),
4.20-4.04 (1H, m), 2.94-2.88 (1H, m), 1.25 (3H, t),
1.0-0.8 (3H, m);

IR (chloroform solution): $\nu=3500, 2930, 1730, 1720, 1370,$

10 965 cm^{-1} ;

Mass: $m/e=380$ (M^+), 362, 344.

By the same procedure as described in Reference
Example 7, the following compounds were prepared.

(a) (13E)-(9 α ,15S)-11-oxo-9,15-dihydroxyprost-13-enoic
15 acid ethyl ester (i.e. PGD₁ ethyl ester)

Starting material: PGD₁ (prepared by the method as described
in Example 2 [B] in the specification of
the Japanese Patent Kokoku No. 54-32773);

TLC (chloroform:tetrahydrofuran:acetic acid=10:2:1): $R_f=0.50$;

20 NMR: $\delta=5.7-5.3$ (2H, m), 4.5 (1H, m), 4.10 (2H, q), 4.21-4.02
(1H, m), 0.90 (3H, t);

IR: $\nu=3420, 2930, 1730, 1720\text{ cm}^{-1}$;

Mass: $m/e=364, 346$.

(b) (5Z,13E)-(9 α ,15S,17S)-11-oxo-9,15-dihydroxy-17,20-
25 dimethylprosta-5,13-dienoic acid ethyl ester (i.e.
17S,20-dimethyl-PGD₂ ethyl ester)

Starting material: 17S,20-dimethyl-PGD₂ prepared in Reference

Example 6;

TLC (chloroform:tetrahydrofuran:acetic acid=10:2:1): R_f=0.50;

NMR: δ =5.75-5.35 (4H, m), 4.53-4.40 (1H, m), 4.13 (2H, q),

5 4.20-4.03 (1H, m), 2.94-2.88 (1H, m), 1.0-0.8 (6H, m);

IR: ν =3500, 2930, 1730, 1720 cm⁻¹;

Mass: m/e=408, 390, 372.

Example 1

(5Z,9Z,13E)-(15S,17S)-11-oxo-15-hydroxy-17,20-dimethylprosta-
10 5,9,13-trienoic acid (i.e. 17S,20-dimethyl-9-deoxy- Δ^9 -PGD₂)

To a solution of 53 mg of the PGD₂ compound
(prepared in Reference Example 6) in 0.7 ml of ethanol was
added 70 ml of a tris hydrochloric acid buffer solution
(prepared from 17.5 ml of a 0.2M aqueous solution of
15 tris(hydroxymethyl)aminomethane, 31.5 ml of a 0.1N
hydrochloric acid and 21 ml of water) (pH=7.2) and the
mixture was stirred for 48 hours at 37°C. The reaction
mixture was extracted with 30 ml of ethyl acetate three times
(total: 90 ml) and the extract was washed with a saturated
20 aqueous solution of sodium chloride, dried over anhydrous
magnesium sulfate and concentrated under reduced pressure.
The residue was purified by column chromatography on silica
gel (eluent: n-hexane:ethyl acetate=1:1) to give 5 mg of the
title compound having the following physical characteristics:

TLC (chloroform:tetrahydrofuran:acetic acid=30:6:1): Rf=0.47;

NMR: δ =7.63 (1H, dd), 6.18 (1H, dd), 5.72-5.35 (4H, m),

4.20-4.05 (1H, m), 1.00-0.80 (6H, m);

IR: ν =3370, 2920, 1705, 1580 cm^{-1} ;

5 Mass: m/e=362, 344.

By the same procedure as described in Example 1,
the following compounds were prepared.

- (a) (5Z,9Z,13E)-(15S)-11-oxo-15-hydroxy-15-(3-propylcyclopentyl)-16,17,18,19,20-pentanoic acid i.e. 15-(3-propylcyclopentyl)-16,17,18,19,20-pentanoic acid
10 deoxy- Δ^9 -PGD₂

Starting material: the PGD₂ compound prepared in Reference
Example 6(a);

15 TLC (chloroform:tetrahydrofuran:acetic acid=30:6:1): Rf=0.49;

NMR: δ =7.64 (1H, dd), 6.17 (1H, dd), 5.75-5.35 (4H, m),

4.20-4.03 (1H, m), 0.88 (3H, t);

IR: ν =3360, 2920, 1705, 1582 cm^{-1} ;

Mass: m/e=374, 356.

- 20 (b) (5Z,9Z,13E)-(15S,17S)-11-oxo-15-hydroxy-17,20-dimethylprosta-5,9,13-trienoic acid ethyl ester
i.e. 17S,20-dimethyl-9-deoxy- Δ^9 -PGD₂ ethyl ester

Starting material: 17S,20-dimethyl-PGD₂ ethyl ester prepared
in Reference Example 7(b);

25 NMR: δ =7.63 (1H, dd), 6.17 (1H, m), 5.75-5.35 (4H, m),

4.30-3.95 (3H, m), 1.00-0.80 (6H, m);

IR: $\nu=3400, 2920, 1738, 1580 \text{ cm}^{-1}$;

Mass: $m/e=390, .372$.

Example 2

(5Z,9Z,14EZ)-(17S)-11-oxo-17,20-dimethylprosta-5,9,12,14-
5 tetraenoic acid

A mixture of 11 mg of the PGD₂ compound (prepared in Reference Example 6), 0.28 ml of 1N hydrochloric acid and 0.28 ml of tetrahydrofuran was refluxed for 20 minutes. To the reaction mixture was added 50 ml of diethyl ether and
10 the solution thus obtained was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: n-hexane:ethyl acetate=2:1) to give 3 mg of the
15 title compound having the following physical characteristics: TLC (chloroform:tetrahydrofuran:acetic acid=30:6:1): $R_f=0.64$; NMR: $\delta=7.48$ (1H, dd), 6.97 (1H, d), 6.47-6.16 (3H, m), 5.56-5.30 (2H, m), 3.64-3.51 (1H, m), 1.00-0.80 (6H, m);
20 IR: $\nu=2920, 1727, 1702, 1626 \text{ cm}^{-1}$;
Mass: $m/e=344$.

By the same procedure as described in Example 2, the following compounds were prepared.

(a) (5Z,9Z,14EZ)-11-oxo-15-(3-propylcyclopentyl)-

16,17,18,19,20-pentanoorprosta-5,9,12,14-tetraenoic
acid.

Starting material: the PGD₂ compound prepared in Reference

Example 6(a);

5 TLC (chloroform:tetrahydrofuran:acetic acid=30:6:1): Rf=0.64;

NMR: δ =7.49 (1H, dd), 6.97 (1H, d), 6.47-6.16 (3H, m),

5.56-5.32 (2H, m), 3.64-3.50 (1H, m), 0.89 (3H, t);

IR: ν =2920, 1726, 1703, 1625 cm⁻¹;

Mass: m/e=356.

10 (b) (5Z,9Z,14EZ)-11-oxo-16-phenyl-17,18,19,20-
tetranorprosta-5,9,12,14-tetraenoic acid

Starting material: the PGD₂ compound prepared in Reference

Example 6(b);

TLC (chloroform:tetrahydrofuran:acetic acid=30:6:1): Rf=0.62;

15 NMR: δ =7.55-7.11 (6H, m), 6.97 (1H, d), 6.51-6.16 (3H, m),

5.57-5.30 (2H, m);

IR: ν =2920, 1728, 1703, 1625 cm⁻¹;

Mass: m/e=336.

(c) (5Z,9Z,14EZ)-11-oxo-16-(3-chlorophenoxy)-
20 17,18,19,20-tetranorprosta-5,9,12,14-tetraenoic
acid

Starting material: the PGD₂ compound prepared in Reference

Example 6(c);

TLC (chloroform:tetrahydrofuran:acetic acid=30:6:1): Rf=0.63;

25 NMR: δ =7.51-6.70 (6H, m), 6.48-6.20 (3H, m), 5.61-5.31

(2H, m);

IR: $\nu=2930, 1728, 1702, 1625, 1600 \text{ cm}^{-1}$;

Mass: $m/e=388, 386$.

(d) (5Z,9Z,14EZ)-11-oxoprost-5,9,12,14-tetraenoic acid

Starting material: PGD₂;

5 TLC (chloroform:tetrahydrofuran:acetic acid=30:6:1): $R_f=0.62$;

NMR: $\delta=7.47$ (1H, dd), 6.96 (1H, d), $6.46-6.15$ (3H, m),

$5.55-5.28$ (2H, m), $3.65-3.52$ (1H, m), 0.90 (3H, t);

IR: $\nu=3600-2400, 2920, 1725, 1700, 1625 \text{ cm}^{-1}$;

Mass: $m/e=316$.

10 (e) (9Z,14EZ)-11-oxoprost-9,12,14-trienoic acid

Starting material: PGD₁;

TLC (chloroform:tetrahydrofuran:acetic acid=30:6:1): $R_f=0.63$;

NMR: $\delta=7.46$ (1H, dd), 6.95 (1H, d), $6.46-6.14$ (3H, m),

$3.62-3.50$ (1H, m), 0.90 (3H, t);

15 IR: $\nu=2920, 1724, 1700, 1624 \text{ cm}^{-1}$;

Mass: $m/e=318$.

(f) (5Z,9Z,14EZ)-11-oxoprost-5,9,12,14-tetraenoic acid

ethyl ester

Starting material: PGD₂ ethyl ester prepared in Reference

20 Example 7;

NMR: $\delta=7.47$ (1H, dd), 6.96 (1H, d), $6.46-6.15$ (3H, m),

$5.54-5.27$ (2H, m), 4.10 (2H, q), 3.58 (1H, m),

0.90 (3H, t);

IR: $\nu=2920, 1738, 1725, 1626 \text{ cm}^{-1}$;

25 Mass: $m/e=344$.

(g) (9Z,14EZ)-11-oxoprost-9,12,14-trienoic acid ethyl

ester

Starting material: PGD₁ ethyl ester prepared in Reference

Example 7(a);

NMR: δ =7.48 (1H, dd), 6.95 (1H, d), 6.46-6.14 (3H, m), 4.12

5 (2H, q), 0.90 (3H, t);

IR: ν =2920, 1738, 1726, 1627 cm⁻¹;

Mass: m/e=346.

(h) (5Z,9Z,14EZ)-(17S)-11-oxo-17,20-dimethylprosta-
5,9,12,14-tetraenoic acid ethyl ester

10 Starting material: 17S,20-dimethyl-PGD₂ ethyl ester prepared
in Reference Example 7(b);

NMR: δ =7.47 (1H, dd), 6.96 (1H, dd), 6.46-6.14 (3H, m),

5.54-5.27 (2H, m), 4.10 (2H, q), 3.58 (1H, m),

1.0-0.80 (6H, m);

15 IR: ν =2920, 1735, 1720, 1628 cm⁻¹;

Mass: m/e=372.

(i) (5Z,9Z,14EZ)-11-oxoprosta-5,9,12,14-tetraenoic acid
methyl ester

Starting material: PGD₂ methyl ester (prepared by esterifying

20 a solution of PGD₂ in diethyl ether by
adding a 0.5 M solution of diazomethane in
diethyl ether until the solution was
coloured pale yellow and then
concentrating under reduced pressure);

25 TLC (ethyl acetate:n-hexane=1:3): R_f=0.44;

NMR: δ =7.46 (1H, dd), 6.94 (1H, d), 6.40-6.14 (3H, m),

5.53-5.28 (2H, m), 3.65 (3H, s), 3.57 (1H, m), 0.89
(3H, t);

IR: ν =2940, 1738, 1695, 1632, 1580 cm^{-1} ;

Mass: m/e =330 (M^+), 299, 259.

- 5 (j) (9Z,14EZ)-11-oxoprostanoic acid
methyl ester

Starting material: PGD₁ methyl ester (prepared by esterifying
PGD₁ with diazomethane);

TLC (ethyl acetate:n-hexane=1:2): R_f =0.64;

- 10 NMR: δ =7.50 (1H, dd), 6.91 (1H, d), 6.33 (1H, dd), 6.30-6.18
(2H, m), 3.65 (3H, s), 3.60-3.48 (1H, m);

IR: ν =2925, 1735, 1690, 1630, 1575 cm^{-1} ;

Mass: m/e =332 (M^+), 301, 261.

- (k) (5Z,9Z,14EZ)-11-oxo-16,16-dimethylprosta-5,9,12,14-
15 tetraenoic acid methyl ester

Starting material: 16,16-dimethyl PGD₂ methyl ester [prepared
by esterifying 16,16-dimethyl-PGD₂
prepared in Reference Example 6(d), with
diazomethane];

- 20 TLC (cyclohexane:ethyl acetate=1:1): R_f =0.58;

NMR: δ =7.65-7.40 (1H, m), 7.05-6.90 (1H, m), 6.35 (1H, dd),
6.30-6.10 (2H, m), 5.60-5.25 (2H, m), 3.65 (3H, s),
3.65-3.50 (1H, m), 1.05 (6H, s), 0.85 (3H, t);

IR: ν =2940, 2850, 1730, 1680, 1620, 1425 cm^{-1} ;

- 25 Mass: m/e =358 (M^+), 314, 273.

The present invention includes within its scope pharmaceutical compositions which comprise at least one prostaglandin D derivative of general formula (I) or (II), cyclodextrin clathrate thereof or, when R¹ represents a
5 hydrogen atom, non-toxic salt thereof together with a pharmaceutical carrier or coating.

In clinical practice, for the prevention or the therapy (including therapy to secure remission) against leukemia or solid cancer, the compounds of the present
10 invention will normally be administered systemically or partially; usually by oral or parenteral (e.g. intravenous, subcutaneous or intramuscular) administration.

Solid compositions for oral administration include compressed tablets, pills, dispersible powders and granules.
15 In such solid compositions, one or more of the active compound(s) is, or are, admixed with at least one inert diluent such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone or magnesium metasilicate aluminate.
20 The compositions may also comprise, as is normal practice, additional substances other than inert diluents e.g. lubricating agents such as magnesium stearate, and disintegrating agents, such as cellulose calcium gluconate. The tablets or pills may, if desired, be made into enteric
25 film-coated or gastric film-coated tablets or pills, such as sugar-coated, gelatin-coated, hydroxypropylcellulose-coated

or hydroxypropylmethylcellulose phthalate-coated tablets or pills; two or more layers may be used.

The compositions for oral administration also include capsules of absorbable material such as gelatin,
5 containing one or more of the active substances with or without the addition of diluents or excipients.

Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents
10 commonly used in the art such as distilled water or ethanol. Besides inert diluents such compositions may also comprise adjuvants such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents.

Other compositions for oral administration include
15 spray compositions which may be prepared by known methods and which comprise at least one compound of the present invention.

Preparations according to the invention for parenteral administration include sterile aqueous or
20 non-aqueous solutions, suspensions or emulsions. Examples of aqueous solvents or suspending media are distilled water for injection and physiological salt solution. Examples of non-aqueous solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive
25 oil, alcohols such as ethanol, and Polysorbate 80 (registered Trade Mark). These compositions may also include adjuvants

such as preserving, wetting, emulsifying and dispersing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation.

- 5 They may also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Other compositions include, for parenteral administration, liquids for external use, and endermic
10 liniments such as ointments; suppositories for rectal administration; and pessaries for vaginal administration. Such compositions are prepared by known methods.

The percentage of active ingredient in the compositions of the invention may be varied, it being
15 necessary that it should constitute a proportion such that a suitable dosage for the therapeutic effect desired shall be obtained. Obviously several unit dosage forms may be administered at about the same time. In general, the preparations should normally contain at least 0.025% by
20 weight of active substance when required for administration by injection; for oral administration the preparations will normally contain at least 0.1% by weight of active substance.

The dose to be administered is determined depending upon, for example, age, body weight, symptoms, the desired
25 therapeutic effects, the route of administration, and the duration of the treatment.

In the human adult, the doses per person are generally between 5 mg and 500 mg by oral administration, and between 500 µg and 50 mg by parenteral administration for the prevention or the therapy (including therapy to secure remission) against leukemia or solid cancer, and can be administered up to several times per day.

As mentioned above, the doses to be used depend on various conditions. Therefore, there may be cases in which doses greater than the ranges specified above, or lower than the ranges specified above, may be used.

The following Examples illustrate pharmaceutical compositions according to the invention.

Example 3

A solution of one gram of (5Z,9Z,14EZ)-11-oxoprostanoic acid in 5 ml of ethanol was well mixed with 5 g of microcrystalline cellulose. After drying the mixture sufficiently, 100 mg of magnesium stearate, 20 mg of silicon dioxide, 10 mg of talc, 200 mg of cellulose calcium gluconate (CCG) and further microcrystalline cellulose to produce 10 g of mixture were added. After mixing well to ensure homogeneity the mixture was punched out in conventional manner to obtain 100 tablets each containing 10 mg of the active ingredient.

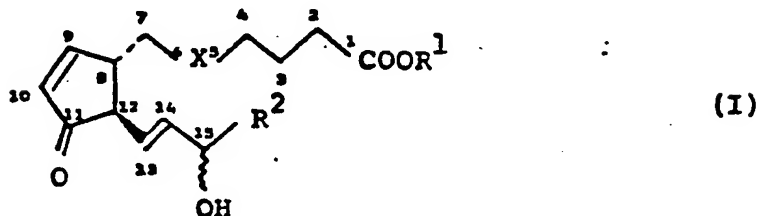
Example 4

A α -cyclodextrin and β -cyclodextrin clathrate of (5Z,9Z,14EZ)-11-oxoprostano-5,9,12,14-tetraenoic acid [prepared by dissolving 2.4 g of α -cyclodextrin and one g of β -cyclodextrin in 300 ml of water, adding thereto 100 mg of (5Z,9Z,14EZ)-11-oxoprostano-5,9,12,14-tetraenoic acid, stirring well and then concentrating under reduced pressure] was dissolved in 150 ml of distilled water for injection. The solution was sterilized by filtration in conventional manner, placed in 1.5 ml portions in 5 ml ampoules and freeze-dried to obtain 100 ampoules of solid composition for injection each containing 1 mg of the active ingredient.

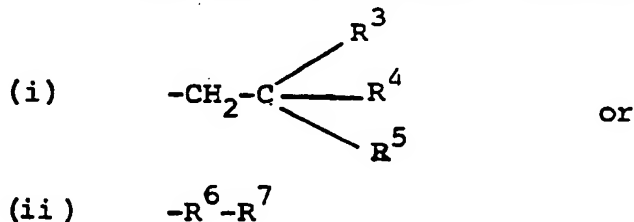
CLAIMS

CONTRACTING STATES: BE, CH, DE, FR, GB, IT, LU, LI, NL, SE

1. A prostaglandin D derivative of the general formula:

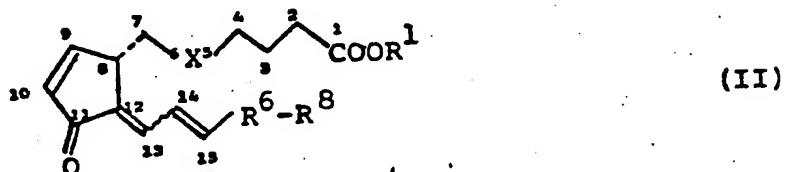


wherein R¹ represents a hydrogen atom or a straight-chain or branched-chain alkyl group of 1 - 12 carbon atoms, R² represents a group of the general formula:



wherein R³ represents a straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms, R⁴ represents a hydrogen atom or a straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms, R⁵ represents a straight-chain or branched-chain alkyl group of 1 - 10 carbon atoms, R⁶ represents a single bond or a straight-chain or branched-chain alkylene group of 1 - 5 carbon atoms, and R⁷ represents a cycloalkyl group of 4 - 7 carbon atoms either unsubstituted or substituted by at least one straight-chain or branched-chain alkyl group of 1 - 8 carbon atoms,

X represents an ethylene group or a cis-vinylene group, the double bond between C₉ - C₁₀ is Z, and the double bond between C₁₃ - C₁₄ is E, or of the general formula:



wherein R¹, R⁶ and X are as hereinbefore defined, R⁸ represents a straight-chain or branched-chain alkyl group of 1 - 8 carbon atoms, a cycloalkyl group of 4 - 7 carbon atoms either unsubstituted or substituted by at least one straight-chain or branched-chain alkyl group of 1 - 8 carbon atoms or represents a phenyl group or phenoxy group either unsubstituted or substituted by at least one halogen atom, trifluoromethyl group or straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms, the double bonds between C₁₂ - C₁₃ and between C₁₄ - C₁₅, which may be in the same or different configuration, are E, Z or a mixture thereof, and the double bond between C₉ - C₁₀ is Z, provided that when R⁶ represents a single bond, R⁸ does not represent a substituted or unsubstituted phenoxy group, and cyclodextrin clathrates of a compound of formula (I) or (II) and, when R¹ in the general formula (I) or (II) represents a hydrogen atom, non-toxic salts thereof.

2. A prostaglandin derivative according to claim 1, wherein R^1 represents a hydrogen atom or a straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms.
3. A compound according to claim 1 or 2, wherein the hydroxy group attached to the 15-position carbon atom is in α -configuration.
4. A prostaglandin derivative according to claim 1, 2 or 3, wherein R^2 represents a 2-methylpentyl, 2-ethylpentyl, 2-methylhexyl, 2-ethylhexyl, 2-methylheptyl or 2-ethylheptyl group; wherein R^2 represents a cyclobutyl, 1-propylcyclobutyl, 1-butylcyclobutyl, 3-ethylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, cyclopentylmethyl, 2-cyclopentylethyl, 3-ethylcyclopentyl, 3-propylcyclopentyl, 3-butylcyclopentyl, cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, 4-methylcyclohexyl, 4-ethylcyclohexyl, 4-propylcyclohexyl or 4-butylcyclohexyl group; wherein R^6-R^8 represents a butyl, pentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylpentyl, 1-ethylpentyl, 2-ethylpentyl, hexyl, 1-methylhexyl, 2-methylhexyl, 1-ethylhexyl, 2-ethylhexyl, heptyl, 2-methylheptyl or 2-ethylheptyl group; wherein R^6-R^8 represents a cyclobutyl, 1-propylcyclobutyl, 1-butylcyclobutyl, 3-ethylcyclobutyl,

3-propylcyclobutyl, cyclopentyl, cyclopentylmethyl, 2-cyclopentylethyl, 3-ethylcyclopentyl, 3-propylcyclopentyl, 3-butylcyclopentyl, cyclohexyl, cyclohexylmethyl, 2-cyclohexylethyl, 4-methylcyclohexyl, 4-ethylcyclohexyl, 4-propylcyclohexyl or 4-butylcyclohexyl group; or wherein R^6-R^8 represents a benzyl, 2-phenylethyl, 4-methylbenzyl, 4-ethylbenzyl, phenoxymethyl, 2-phenoxyethyl, 3-chlorophenoxymethyl, 4-chlorophenoxymethyl, 3-trifluoromethylphenoxymethyl, 4-trifluoromethylphenoxy-methyl, 4-methylphenoxy-methyl or 4-ethylphenoxy-methyl group.

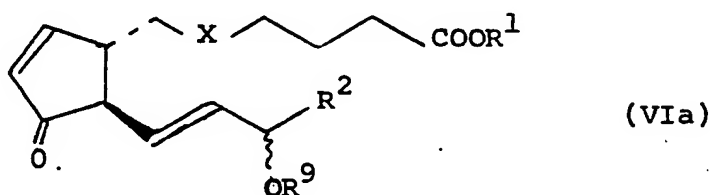
5. A prostaglandin derivative according to claim 4 which is (5Z,9Z,13E)-(15S,17S)-11-oxo-15-hydroxy-17,20-dimethylprosta-5,9,13-trienoic acid, or its methyl or ethyl ester, (5Z,9Z,13E)-(15S)-11-oxo-15-hydroxy-15-(3-propylcyclopentyl)-16,17,18,19,20-pentanoorprosta-5,9,13-trienoic acid, or its methyl or ethyl ester, (5Z,9Z,14EZ)-11-oxoprosta-5,9,12,14-tetraenoic acid, or its methyl or ethyl ester, (9Z,14EZ)-11-oxoprosta-9,12,14-trienoic acid, or its methyl or ethyl ester, (5Z,9Z,14EZ)-(17S)-11-oxo-17,20-dimethylprosta-5,9,12,14-tetraenoic acid, or its methyl or ethyl ester, (5Z,9Z,14EZ)-11-oxo-16,16-dimethylprosta-5,9,12,14-tetraenoic acid, or its methyl or ethyl ester, (5Z,9Z,14EZ)-11-oxo-15-(3-propylcyclopentyl)-16,17,18,19,20-pentanoorprosta-5,9,12,14-tetraenoic acid, or its methyl or ethyl ester, (5Z,9Z,14EZ)-11-oxo-

16-phenyl-17,18,19,20-tetranorprosta-5,9,12,14-tetraenoic acid, or its methyl or ethyl ester, or (5Z,9Z,14EZ)-11-oxo-16-(3-chlorophenoxy)-17,18,19,20-tetranorprosta-5,9,12,14-tetraenoic acid, or its methyl or ethyl ester.

6. A cyclodextrin clathrate of a prostaglandin derivative claimed in claim 5 or a non-toxic salt of a prostaglandin derivative acid as claimed in claim 5.

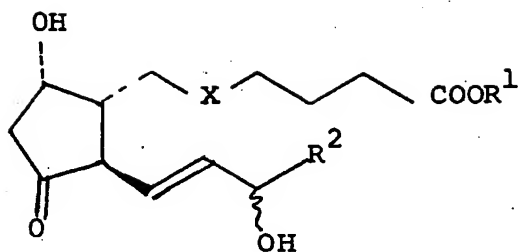
7. A process for the preparation of prostaglandin D derivatives as claimed in claim 1, which comprises, when the prostaglandin derivative conforms to the general formula (I) wherein the various symbols are as defined in claim 1,

(i) the hydrolysis under acidic conditions of a compound of the general formula:



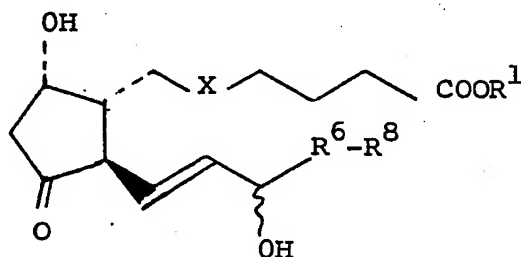
wherein R^9 represents a tetrahydropyran-2-yl group, a tetrahydrofuran-2-yl group either unsubstituted or substituted by at least one alkyl group, or a 1-ethoxyethyl group, and the other symbols are as defined in claim 1, or (ii) dehydration of a compound of the general formula:

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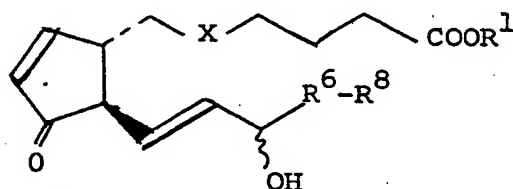


(IIIa)

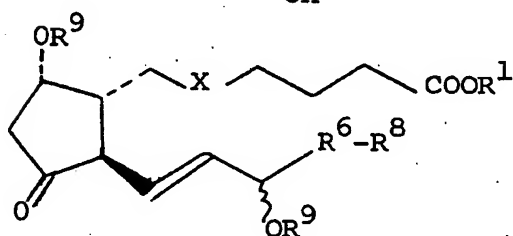
(wherein the various symbols are as defined in claim 1)
 under mild conditions or, when the prostaglandin D
 derivative conforms to the general formula (II) wherein
 the various symbols are as defined in claim 1,
 (iii) the reaction of a compound of the general formula:



(III)

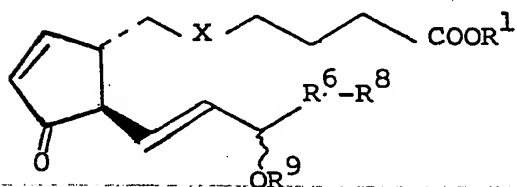


(IV)



(V)

or



(VI)

wherein R^9 is as hereinbefore defined and the other symbols are as defined in claim 1, with an aqueous acid solution, optionally followed by the step of converting a prostaglandin derivative of general formula (I) or (II) wherein R^1 represents a hydrogen atom into an alkyl ester having from 1 to 12 carbon atoms in the alkyl radical or into a non-toxic salt, or by the step of converting a prostaglandin derivative of general formula (I) or (II) into a cyclodextrin clathrate thereof.

8. A pharmaceutical composition which comprises, as active ingredient at least one prostaglandin derivative of the general formula (I) or (II) depicted in claim 1, wherein the various symbols are as defined in claim 1, or a cyclodextrin clathrate thereof, or, when R^1 in formula (I) or (II) depicted in claim 1 represents a hydrogen atom, a non-toxic salt thereof, in association with a pharmaceutical carrier or coating.

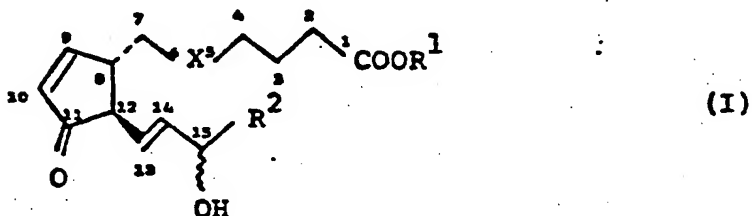
9. A compound of the general formula (VIa), (V) or (VI) depicted in claim 7 wherein R^9 is as defined in claim 7 and the other symbols are as defined in claim 1.

10. A prostaglandin derivative or cyclodextrin clathrate thereof or non-toxic salt thereof, as claimed in claim 1, for use in the prevention or therapy of leukemia or solid cancer.

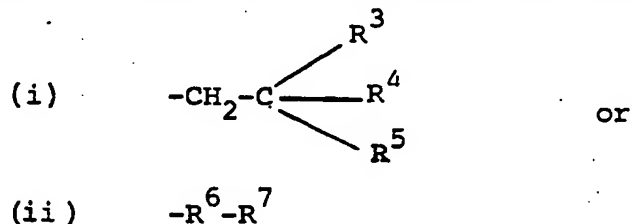
CLAIMS

CONTRACTING STATE: AT.

1. A process for the preparation of a prostaglandin D derivative of the general formula:

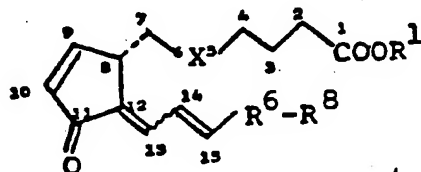


wherein R¹ represents a hydrogen atom or a straight-chain or branched-chain alkyl group of 1 - 12 carbon atoms, R² represents a group of the general formula:



wherein R³ represents a straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms, R⁴ represents a hydrogen atom or a straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms, R⁵ represents a straight-chain or branched-chain alkyl group of 1 - 10 carbon atoms, R⁶ represents a single bond or a straight-chain or branched-chain alkylene group of 1 - 5 carbon atoms, and R⁷ represents a cycloalkyl group of 4 - 7 carbon atoms either unsubstituted or substituted by at least one straight-chain or branched-chain alkyl group of 1 - 8 carbon atoms.

X represents an ethylene group or a cis-vinylene group, the double bond between C₉ - C₁₀ is Z, and the double bond between C₁₃ - C₁₄ is E, or of the general formula:

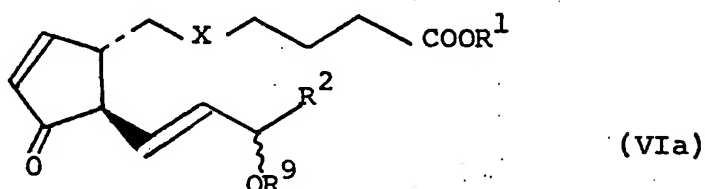


(II)

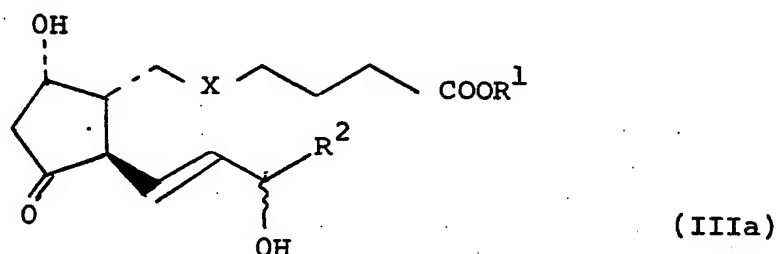
wherein R¹, R⁶ and X are as hereinbefore defined, R⁸ represents a straight-chain or branched-chain alkyl group of 1 - 8 carbon atoms, a cycloalkyl group of 4 - 7 carbon atoms either unsubstituted or substituted by at least one straight-chain or branched-chain alkyl group of 1 - 8 carbon atoms or represents a phenyl group or phenoxy group either unsubstituted or substituted by at least one halogen atom, trifluoromethyl group or straight-chain or branched-chain alkyl group of 1 - 4 carbon atoms, the double bonds between C₁₂ - C₁₃ and between C₁₄ - C₁₅, which may be in the same or different configuration, are E, Z or a mixture thereof, and the double bond between C₉ - C₁₀ is Z, provided that when R⁶ represents a single bond, R⁸ does not represent a substituted or unsubstituted phenoxy group, or cyclodextrin clathrate of a compound of formula (I) or (II) or, when R¹ in the general formula (I) or (II) represents a hydrogen atom, a non-toxic salt thereof which comprises, when the prostaglandin

derivative conforms to general formula (I), wherein the various symbols are as hereinbefore defined:

(i) the hydrolysis under acidic conditions of a compound of the general formula:

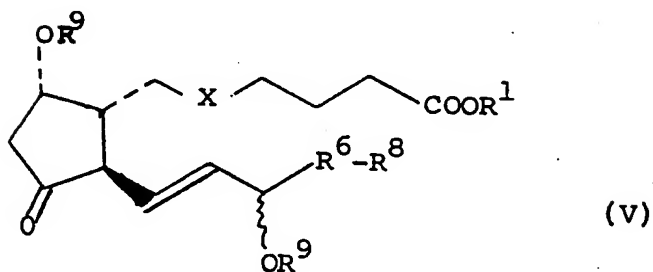
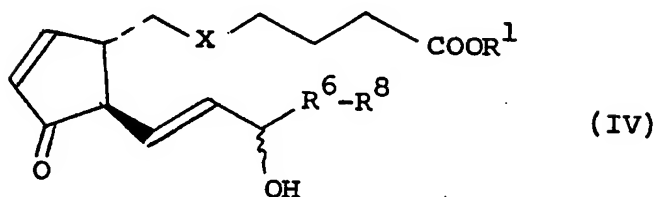
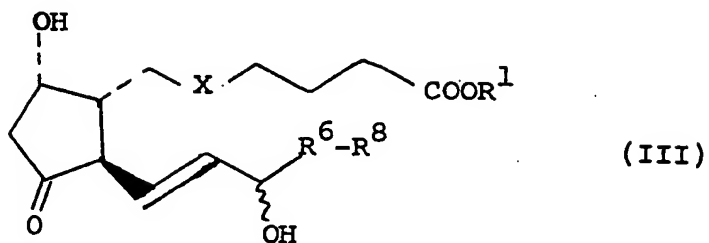


wherein R^9 represents a tetrahydropyran-2-yl group, a tetrahydrofuran-2-yl group either unsubstituted or substituted by at least one alkyl group, or a 1-ethoxyethyl group, and the other symbols are as hereinbefore defined, or (ii) dehydration of a compound of the general formula:

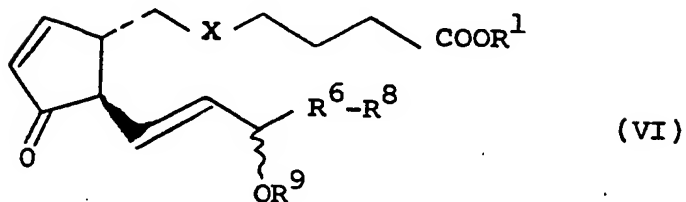


(wherein the various symbols are as hereinbefore defined) under mild conditions; or, when the prostaglandin derivative conforms to the general formula (II), wherein the various symbols are as hereinbefore defined,

(iii) the reaction of a compound of the general formula:



or



(wherein the various symbols are as hereinbefore defined) with an aqueous acid solution followed, if desired, (a) by the step of converting a prostaglandin derivative of general formula (I) or (II) wherein R^1 represents a hydrogen atom into an alkyl ester having from 1 to 12 carbon atoms in the alkyl radical or into a non-toxic salt, or (b) by the step of converting a prostaglandin derivative of general formula (I) or (II) into a cyclodextrin clathrate thereof.

2. Process according to claim 1 wherein the symbol R^9 in the compound of general formula (VIa) represents a tetrahydropyran-2-yl group and the other symbols are as defined in claim 1.

3. A process according to claim 1 or 2, wherein the hydrolysis under acidic conditions of the compound of the general formula (VIa), wherein the various symbols are as defined in claim 1 or 2, is carried out using a mixture of dilute hydrochloric acid and tetrahydrofuran, a mixture of dilute hydrochloric acid and methanol, a mixture of acetic acid, water and tetrahydrofuran, a mixture of phosphoric acid, water and tetrahydrofuran, or a mixture of p-toluenesulphonic acid and anhydrous methanol.

4. A process according to claim 1, wherein the dehydration under mild conditions of a compound of the general formula IIIa, wherein the various symbols are

as defined in claim 1, is carried out by reaction with a tris hydrochloric acid buffer solution at a temperature of 30-40°C.

5. A process according to claim 1, wherein the reaction of a compound of the general formula (III), (IV), (V) or (VI), wherein the various symbols are as defined in claim 1, with an aqueous acid solution is carried out in tetrahydrofuran using 1N hydrochloric acid at the reflux temperature of the reaction mixture.

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